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DISEASES OF THE CHEST

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EDITORIAL

THE last decade has witnessed stupendous changes in all branches of thoracic medicine, including respiratory tuberculosis.

Modern chemotherapeutic drugs have made necessary a complete reappraisal of certain intrathoracic diseases, their causation, and preventive, diagnostic and therapeutic measures to combat them. Combined and prolonged chemotherapy has eliminated from pulmonary tuberculosis its dreaded stigma, while the antibiotics have revolutionised the prognosis and management of the "pneumonias." In addition, newer scourges, like cancer of the lung and chronic bronchitis, leading to emphysema and pulmonary heart disease, must come within the purview of this journal. Again, the remarkable progress in thoracic surgery, the radiology of the chest, applied respiratory physiology and anæsthesia as it affects the lungs, heart and circulation, and the anatomical and functional relationship of all the organs within the thoracic cage, come within its scope. Not least are the changing patterns of disease which need to be considered and, where necessary, integrated with general medicine.

Widespread and sometimes indiscriminate use of antibiotic and other drugs has its hazards and may be a possible factor in the apparent increase of certain "collagen" diseases and of some pulmonary fibroses of uncertain ætiology. Unrestricted air travel, annihilating distance, may introduce diseases, for example certain mycoses, previously rarely encountered in this country, while the tuberculosis rampant in backward countries can all too easily be transferred to this island and mock at the complacency that is developing in some quarters.

For reasons such as these the Editorial Board has decided to change the title of this Journal to "British Journal of Diseases of the Chest" and to erect yet another landmark in its history.

The pioneering of a journal in a special field in 1907, when specialisation was at a very early stage of evolution, required, as Sir Robert Young affirmed at our Golden Jubilee Dinner, great courage, vision and enthusiasm on the part of the first Editor, Dr. T. N. Kelynack, and the publishers. Dr. Kelynack remained Editor for twenty-seven years and was succeeded by Dr. L. S. T. Burrell, who sought to widen the scope of the Journal. Next, Dr. Clifford Hoyle not only maintained the independent nature of the Journal during his thirteen years in the editorial chair but, in 1943, gave expression to the needs and trends of the time by adding "Diseases of the Chest" to the title. In 1956 the Journal reached its Golden Jubilee and celebrated the occasion with a special issue, and we hope that the new epoch we are inaugurating with a change of designation will meet with the general approval of our readers.

The sphere of activity of the chest physician of to-day embraces the social, preventive, diagnostic and therapeutic facets of all intrathoracic diseases.

We are proud of and grateful for the messages we have already received

which would indeed appear to justify our decision. We are particularly happy to include in this issue the good wishes of Sir John Charles, Chief Medical Officer of the Ministry of Health, who in a few succinct words portrays the position of tuberculosis to-day and the function of the chest physician; of Professor Robert Platt, President of the Royal College of Physicians, who encourages us to go on from tuberculosis to seek new fields to conquer; of Sir Robert Young, the Grand Old Man of chest medicine and a lifelong friend of the Journal; and of Sir Clement Price Thomas, who comments so trenchantly and encouragingly on the surgical aspects of diseases of the heart, lungs and mediastinum.

It will be our most earnest endeavour that none of these good wishes shall fall on deaf ears and that by opening our pages to workers in wider fields, even of opposing views, we shall help to lay the ghost of yet more scourges of the human race. In this age of a National Health Service we must never forget that " to know disease is the beginning of health " (Cervantes).

Original contributions from many parts of the globe appear in this issue, including a monograph on Laennec demonstrating, we trust, the breadth and catholicism that are the present and future aim of the BRITISH JOURNAL OF DISEASES OF THE CHEST.

GREETINGS

From Sir John Charles, K.C.B.

Chief Medical Officer, Ministry of Health

On the present occasion these few prefatory words are both a foreword and a forewind—the auspicious zephyr which blows a ship forward on its course.

For fifty-odd years this Journal has served its readers and its generation well, and has established its place and disseminated its influence all over the world. That it should seek now to relinquish one half of its title, and sail under the shorter and yet more comprehensive name of "British Journal of Diseases of the Chest" is fully understandable. Tuberculosis, whether respiratory or non-respiratory, is no longer the universal, implacable and irresistible visitor which brought death and misery into innumerable homes in this country. Its ravages are not yet stayed and there are many countries where it remains the most clamant of public health problems. But it would be myopic to suggest that tuberculosis, which registered some 25,339 deaths in 1938 and 4,784 in 1957, has not suffered a sea-change in the two intervening decades. And more particularly is it clear that the points of emphasis are no longer stationary, when we note that in the period mentioned cancer of the lung had increased its tally of mortality from 4,658 deaths to 19,119.

The chest physician of to-day, like his peers in many other branches of medicine, works in a world of increasing pathological and therapeutic complexity. He ranges over a field in which new ætiological discoveries, modern respiratory physiology, a vast therapeutic armamentarium, and the greatly enhanced resources of surgery have complicated his task. But the diagnostic and therapeutic complications—through the increased precision which they ultimately procure, all contribute to the greater benefit of the patient. Hence this re-orientation of our old Journal. While it will seek to achieve, and successfully, a broader outlook, it will still remain for its readers that familiar repository of experience, understanding and wisdom which they have learned to treasure. May it long continue to serve as an outstanding forum of clinical and scientific enlightenment, and of good counsel.

From Professor Robert Platt

President Royal College of Physicians of London

EVOLUTION BY NATURAL SELECTION

It is always good to hear of a man expanding his interests, especially after the age of 50, and it is good to hear of a journal doing the same thing. Looked at in one way, this may be thought to be a rare phenomenon in an age of

specialisation, but I think a more proper assessment of present tendencies shows that the days when a specialist knew more and more about less and less are over, even if they ever existed. Whatever may be your branch of study, at no time has it been so necessary to know at least some of the applications of knowledge acquired from quite other fields. How different, for instance, is the equipment, both technical and intellectual, of the anæsthetist of to-day from that of his predecessor of even twenty-five years ago. How much wider the necessary extent of his knowledge of physics and chemistry, physiology and pharmacology. So it is with all specialities, the old barriers and with them the old jealousies are being broken down.

The change of name which we celebrate in this Journal has come about not only through this general widening of interests but also through successes in the conquest of tuberculosis, which having closed so many beds in sanatoria have now reduced the proportion of contributions to the literature.

It is nearly 100 years since Darwin, in 1859, published the " Origin of Species." The new look of this old Journal is an example of how new species emerge from the old by the process of natural selection. It is a healthy evolution.

The conquest of tuberculosis is a matter for congratulation. We must not forget, however, that this kind of triumph is no new phenomenon of the present century. A British Journal of Cholera and Smallpox, had there been one, would have had to widen its interests a long time ago if it were to remain viable.

It has been wisely said that the evidence against cigarette smoking as a cause of bronchial carcinoma is quite as strong as the evidence which led John Snow to remove the handle of the Broad Street pump and stop the cholera epidemics. The remedy to the bronchial carcinoma epidemic is not so simple to apply, but let us not pretend that we do not know what it is.

From Sir Robert Young, C.B.E.

Consulting Physician to the Middlesex and Brompton Hospitals, London

It gives me great pleasure to congratulate this Journal on its change of name, which is in harmony with the general trend of all institutions and journals dealing with pulmonary diseases. Most, if not all, of the hospitals concerned with these diseases have made a similar change and enlarged and modified their departments. The Tuberculosis Dispensaries have become Chest Clinics and the Tuberculosis Officers of the days before the National Health Act are now called Chest Physicians. The N.A.P.T. is about to change to the " Chest and Heart Association." This Journal recognised the necessity for the change as long ago as 1943, when it added " Diseases of the Chest " to its title, while Dr. Clifford Hoyle was Editor.

There is unfortunately an impression current among the public, and even some medical men, that the problem of pulmonary tuberculosis in this country has been solved and that this form of tuberculosis is well on the way to

eradication. It cannot be too strongly urged that at present this disease is controlled, but by no means conquered, and that it cannot be until the infective open cases are discovered and dealt with. It is, however, encouraging that serious efforts to achieve this are in operation.

While we must recognise the profound results of the discovery of the antibiotics in the treatment of chest diseases—at first the discovery of penicillin by Fleming and its effects on the treatment of pneumonia and other coccal infections, and the later introduction of streptomycin by Waksman, with the additions of PAS and INAH in tuberculosis—it would seem they are not the ultimate solution, since they are antibacterial and not immunity-producing agents. BCG has established its use as a valuable effort in this direction, but it cannot be regarded as the complete and final answer; it is to be hoped that some preparation can be found to give the lasting immunity conferred on so many by healed symptomless lesions.

I have been fortunate in knowing the Journal since its inception and enjoying the friendship of its successive editors—Dr. Kelynack, Dr. L. S. T. Burrell, Dr. Clifford Hoyle and Dr. Philip Ellman—each of whom has left a personal impress on its form and fortunes, the present Editor, Dr. Philip Ellman, perhaps most of all. He has had the difficult task of steering it through the antibiotic period, during which his great clinical and administrative experience has been of the utmost value in the selection of original articles for publication.

It will be recognised that the change of name does not indicate a change of policy but an adjustment of perspective. Tuberculosis is still a national and even more an international problem, requiring constant study, the more so that our increasing experience and success may be of great value to less fortunate areas, where this disease is still rife and not controlled.

Chest diseases present many other problems of great importance and interest, notably cancer of the bronchi, the acute and chronic bronchial and pulmonary infections, including the fungous and virus diseases, and the study of allergic conditions, notably asthma, all of which are receiving the concentrated attention of many specialist investigators.

I feel sure the change of title is of good augury for the continued usefulness and success of this Journal.

From Sir Clement Price Thomas, K.C.V.O.

Consulting Surgeon to the Westminster and Brompton Hospitals, London

Some years ago, the BRITISH JOURNAL OF TUBERCULOSIS added to its title the words " and Diseases of the Chest." This it was impelled to do because of the widening of interest in other pulmonary diseases which more and more were becoming amenable to treatment.

The present change, by which the subsidiary title becomes the main one, is more than justifiable in that it comprehends all those conditions which preoccupy those who are interested in chest disease, whether physicians,

surgeons or members of any of the other branches of the profession engaged in this field.

A quarter of a century ago, pulmonary tuberculosis engaged the major part of our interest and, surgically speaking, accounted for at least 60 per cent. of the material treated. To-day, although tuberculosis still demands our close interest and attention, the emphasis has shifted; now malignant disease of the lung and œsophagus and both acquired and congenital heart disease provide the greatest challenge to our action and thinking. One of the chief factors in this change of emphasis has been the introduction of antibacterial therapy. The first beneficial result was the decreased incidence in lung abscess and the greater ease of control of pulmonary infections with the introduction, firstly, of the sulpha drugs and afterwards of penicillin; for example, acute lung abscess, of which, in the early thirties, there were at least three or four cases in our wards undergoing drainage, is now a relatively uncommon disease. It is rarely seen in the acute stage by the surgeon, when it is rightly treated by the physician with chemotherapy, and is only referred to the surgeon when it has reached a chronic phase, and then is treated not by drainage but by resection.

The most dramatic change, however, has followed the discovery of streptomycin and the other anti-tuberculous drugs, the most important result of which, besides controlling the disease in the individual patient, has been their contribution to the general control of the disease in that fewer sputum-positive cases live in the general community, thus decreasing the risk of disseminating infection.

From the surgical point of view this change has been no less dramatic: the number of cases needing surgical intervention has decreased enormously and the type of intervention employed has altered, excisional methods replacing to a large extent the older methods of collapse. These great medical advances have been made *pari passu* with the advances in thoracic surgery. Surgical advance has rested on three great bases: more accurate diagnosis which has largely depended on the phenomenal improvement in radiological technique, the tremendous strides made in the fields of anæsthesia, and lastly, a fuller knowledge and appreciation of respiratory physiology.

These three factors have permitted the surgeon to elaborate his technique; firstly, more accurate pre-operative diagnosis has enabled him to plan his intervention with extraordinary accuracy; it is no longer right and proper to depend on an exploratory thoracotomy for, within certain limits, it is possible with the knowledge at our disposal to plan definitively the procedure to be adopted; secondly, anæsthesia has improved to such a degree that, combined with the benefit of blood transfusion, it is possible to carry out prolonged and difficult operative procedures and maintain the patient's cardio-respiratory state at its pre-operative level throughout and return the patient to bed in a condition little changed from that maintaining before operation. The main improvements in anæsthesia rest largely on a fuller comprehension of the cardio-respiratory needs of the individual, and on the introduction of new anæsthetic agents and technique, which permit the anæsthetists to implement these requirements with reasonable ease.

All these factors have permitted the surgeon to introduce refinements in technique which were quite impossible of achievement in the era before the above factors were available. The summation of all these things is that surgery can be carried out with a markedly diminished mortality and morbidity rate.

It is not surprising, therefore, that the field of surgical intervention has been increased. Oesophageal surgery which fifteen years ago was fraught with danger to the patient and infinite anxiety to the surgeon, is now undertaken with reasonable confidence, and some of the operations on the heart are now routine procedures, conducted in skilled hands with confidence and with excellent results.

He would be a bold man who would set any limits to the advances which are now taking place. Our knowledge of so many things is, to say the least, sketchy. The factors underlying the onset of emphysema, the control of asthma, the collagenous diseases and many other problems still beset us and act as a stimulus to our thinking.

All these considerations are a sufficient warranty for the change in name and emphasis of this Journal which for more than fifty years has played a prominent part in disseminating knowledge in this particular field.

The celebration of its Golden Jubilee in 1956 leads one to hope that its sphere of usefulness will continue until one day it may celebrate its centenary.

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HISTOLOGICAL CHANGES IN THE LUNG IN DISEASES ASSOCIATED WITH PULMONARY VENOUS HYPERTENSION

By Donald Heath* (*Mayo Foundation*†)
and Jesse E. Edwards (*Section of Pathologic Anatomy*)
From the Mayo Clinic and Mayo Foundation, Rochester, Minnesota, U.S.A.

Characteristic changes develop in the pulmonary arteries, veins and parenchyma of patients who have chronic pulmonary venous hypertension from birth or acquire it in adult life. The changes in the veins and in the parenchyma appear to be a direct result of the elevated blood pressure in the pulmonary veins and venules. The changes in the arteries are related to the resulting pulmonary arterial hypertension. The purpose of this article is to describe these vascular and parenchymal lesions, whose incidence and hæmodynamic significance in association with mitral stenosis and incompetence have long been appreciated (Parker and Weiss, 1936; Larrabee *et al.*, 1949; Becker *et al.*, 1951).

Clinical Material

A histological examination was made of the lungs from 13 patients with diseases associated with pulmonary venous hypertension. The age and sex of the patients are recorded in the table. These cases were considered in three groups.

Group 1 was comprised of 6 patients (cases 1 to 6) who had congenital heart diseases, without cardiac septal defects, that resulted in pulmonary venous hypertension and associated pulmonary arterial hypertension. Included in this group were cardiac malformations that hindered pulmonary venous return, such as cor triatriatum (case 1), congenital mitral stenosis (case 2) and congenital stenosis of all of the pulmonary veins at left atrial ostia (case 3). Also included were a case of constrictive endocardial sclerosis (case 4), a case of congenital mitral incompetence due to a defect of the anterior leaflet of the mitral valve (case 5), and a case of congenital mitral incompetence associated with a corrected transposition of the great vessels and no ventricular septal defect (case 6).

* Dr. Heath was in receipt of a Rockefeller Travelling Fellowship in Medicine while participating in this investigation, which was supported in part by research grant No. H3531 from the National Heart Institute, National Institutes of Health, United States Public Health Service.

† The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

(*Received for publication August* 20, 1958.)

PLATE I

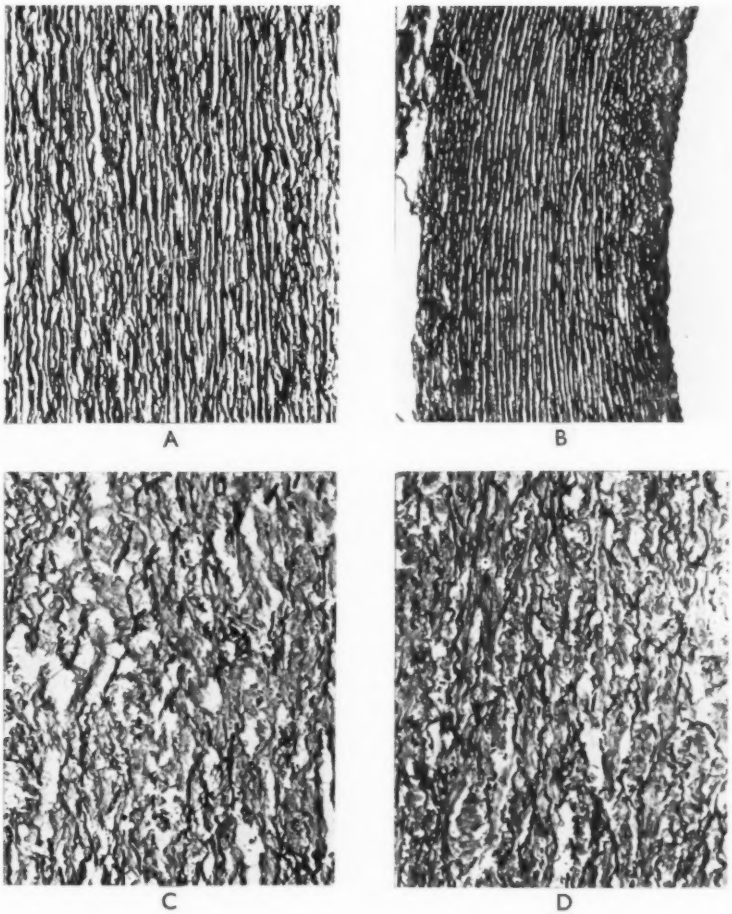


FIG. 1.—Transverse sections of pulmonary trunk stained by the Lawson modification of the Weigert-Sheridan method to demonstrate the configuration of the elastic tissue (all ×90). A. Case 8 (group 2); aortic type. B. Case 4 (group 1); aortic type. C. Case 13 (group 3); pulmonary type. D. Case 11 (group 3); pulmonary type.

To face p. 8

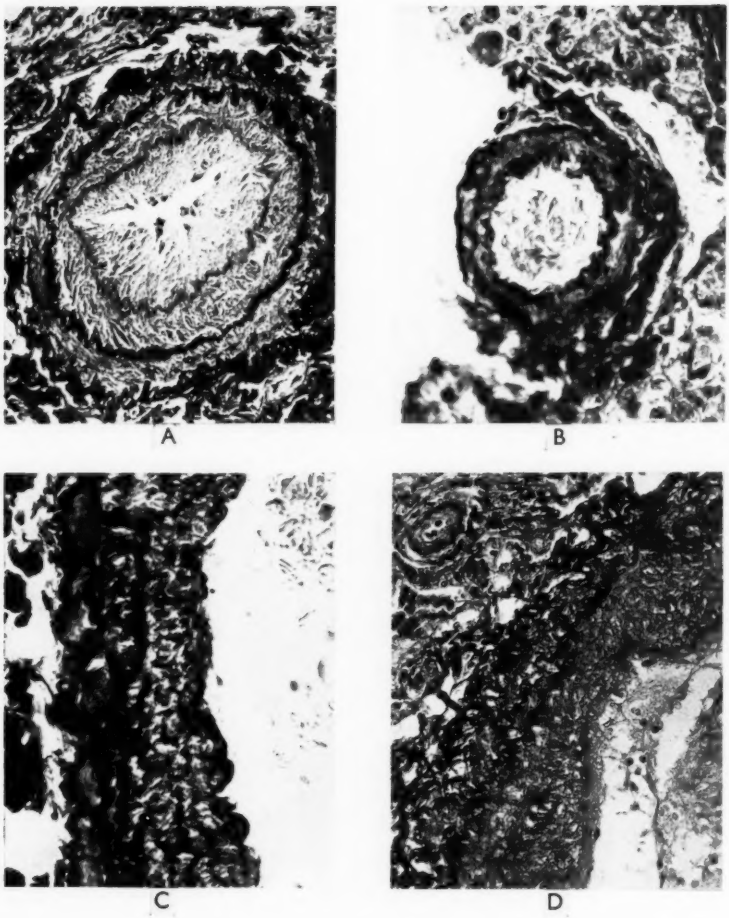
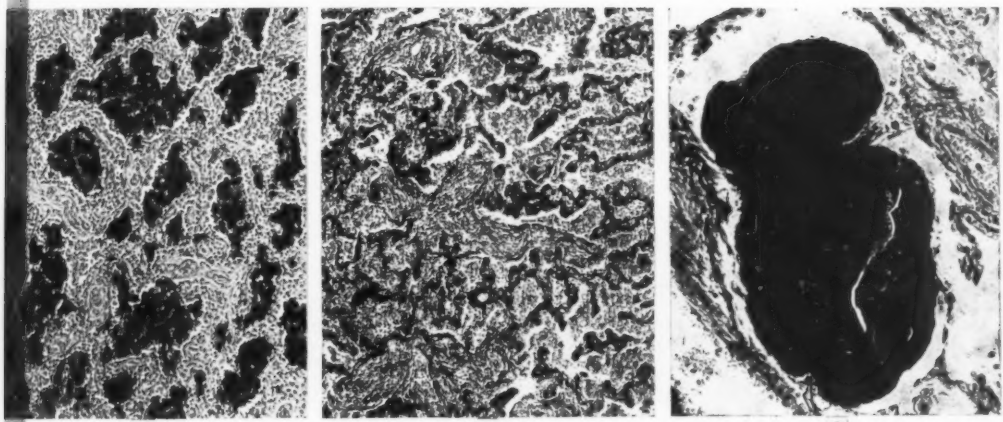


FIG. 2.—Transverse sections of pulmonary vessels stained to demonstrate elastic tissue by Lawson's method and counterstained with Van Gieson's stain (ELVG) to show muscle and collagen. A. Case 11 (group 3); muscular pulmonary artery showing medial hypertrophy and intimal fibrosis (×300). B. Case 1 (group 1); pulmonary arteriole showing muscular media with distinct internal and external elastic laminae (×500). C and D. Part of transverse section of pulmonary vein showing muscular media, with distinct internal and external elastic laminae, resembling wall of an artery. There is severe intimal fibrosis. C. Case 11 (group 3; ×500). D. Case 13 (group 3; ×200).

PLATE III



g. 3.—Pulmonary tissue. A. Case 8 (group 2); section stained by Perls' reagents to demonstrate iron. There is severe lmonary haemosiderosis with numerous collections of haemosiderin containing macrophages in the lung substance <90). B. Case 6 (group 1); organization of intra-alveolar oedema coagulum (ELVG; ×50). C. Case 6 (group 1); spicule of bone (ELVG; ×200).

Group 2 was composed of 3 patients (cases 7 to 9) each of whom had mitral atresia with a narrowly patent foramen ovale and a single ventricle with transposition of the great vessels. Case 9 had in addition a patent ductus arteriosus. While these patients had pulmonary venous hypertension from birth, the associated pulmonary arterial hypertension must be regarded as primarily due to the free communication between the common ventricle and the lesser circulation.

Group 3 consisted of 4 patients (cases 10 to 13) in whom the pulmonary venous hypertension and the associated elevation of pulmonary artery blood pressure were acquired in adult life. The heart diseases responsible for this elevation of pressure were acquired non-rheumatic mitral incompetence, consequent upon either healed bacterial endocarditis (cases 10 and 11) or ruptured mitral chordæ tendineæ (case 12), and granuloma of the mediastinum with stricture of most of the pulmonary veins except those from the right lower lobe (case 13).

In some of the patients the elevated blood pressure in the pulmonary arteries and veins was demonstrated by cardiac catheterisation. In the remainder its existence, although not demonstrated, was regarded as inevitable in view of the nature of the cardiac lesions.

Method

Portions of the pulmonary trunk and the upper and lower lobes of each lung, previously fixed in 10 per cent. formol-saline solution, were paraffin embedded. A transverse section of the pulmonary trunk was stained by Verhoeff's method to demonstrate the elastic tissue. Some sections of lung were stained with hæmatoxylin and eosin and others with a combination of Verhoeff's stain, for elastic tissue, and Van Gieson's stain, to demonstrate muscle and collagen. Perls' stain also was employed in each instance to demonstrate pulmonary hæmosiderosis.

Histological Results (see Table 1)

Structural changes were observed in the pulmonary trunk (Fig. 1*), the muscular pulmonary arteries (Fig. 2A), the arterioles (Fig. 2B), the pulmonary veins (Figs. 2C and 2D), and the pulmonary parenchyma (Fig. 3).

Changes in the Pulmonary Trunk

In the cases in groups 1 and 2 the elastic fibrils in the pulmonary trunk were long and regular, similar to those in the adult aorta, and showed little tendency to branching or fragmentation; they were tightly packed and tended to run parallel to one another (Figs. 1A and 1B). In 2 cases with no septal defects (cases 1 and 5) the configuration of the elastic tissue in the media of the pulmonary trunk was similar to that seen in the fœtal pulmonary trunk, but the individual fibres were not so long and uniform as in the group 2 cases with a free communication between the systemic and pulmonary arterial systems.

* The figures referred to in the text appear on Plates I-III.

The aorta-like pattern was disrupted to some extent by medial necrosis in one of the cases with a common ventricle (case 9). Tissue from the pulmonary trunk was not available in one of the cases in group 1 (case 6). In the cases of group 3, all characterised by the acquisition of pulmonary venous and arterial hypertension in adult life, the arrangement of the elastic fibrils in the media of the pulmonary trunk was that seen in the normal adult major pulmonary arteries (Figs. 1C and 1D; Heath *et al.*, 1958d). The elastic fibrils were short, fragmented and irregular with club-like terminal expansions; they were loosely and haphazardly arranged and showed a great tendency to branching.

TABLE I.—INCIDENCE OF HISTOLOGICAL CHANGES ASSOCIATED WITH HYPERTENSION IN THE PULMONARY ARTERIES AND VEINS IN 13 CASES

Case	*Age, year and sex*	*Pulmonary arteries*		*Pulmonary veins**			
		Type of configuration of elastic tissue in pulmonary trunk†	*Grade of HPVD**	*W*	*X*	*Y*	*Z*
	Group 1. Pulmonary venous hypertension (PVH) from birth, no communication between systemic ventricle and pulmonary circulation						
1	7/12F	Aortic	1	+	0	0	0
2	1 M	Aortic	1	+	+	0	0
3	1 M	Aortic	1	+	+	0	0
4	5 M	Aortic	3	+	+	+	0
5	8 M	Aortic	1	+	0	0	0
6	31 F	—	3	+	+	+	+
	Group 2. Pulmonary venous hypertension from birth, free communication between systemic ventricle and pulmonary circulation						
7	21/12 M	Aortic	1	+	0	0	0
8	14 F	Aortic	2	+	+	0	0
9	15 M	Aortic	4	+	+	+	0
	Group 3. Acquired pulmonary venous hypertension						
10	46 M	Pulmonary	3	+	+	0	0
11	45 F‡	Pulmonary	3	+	+	+	0
12	52 M‡	Pulmonary	3	+	+	+	+
13	26 F‡	Pulmonary	3	+	+	+	0

* Key: HPVD=Hypertensive pulmonary vascular disease.
W =Pulmonary congestion with hæmosiderosis.
X =Changes in vein walls as described in text.
Y =Late changes in the lung substance as described in text.
Z =Spicules of bone in lung.

† Defined by Heath *et al.* (1958d).

‡ These cases have been reported previously (Becker *et al.*, 1951; Edwards and Burchell, 1951).

Changes in the Small Pulmonary Arteries

All the patients studied had hypertensive pulmonary vascular disease. In group 1, the 3 patients 1 year or less in age (cases 1 to 3) and 1 patient 8 years of age (case 5) showed only the earliest histological changes in the pulmonary arteries. The muscular pulmonary arteries with external diameters between 100 and 300 microns in these 4 cases showed an increase in the thickness of the media so that it exceeded the normal, previously determined as 2·8 and 3·1 per cent. of the external diameter for the vessels in the upper and lower lobes and 5·5 to 6·8 per cent. of the external diameter for those of the lingula (Heath and Best, 1958). The muscular arteries greater than 300 microns in diameter also appeared hypertrophied. The arterioles, which are arterial vessels, usually less than 100 microns in diameter with a wall consisting of a single elastic lamina lined by endothelium, except at their origin from a muscular pulmonary artery, were abnormal in having a muscular media between internal and external elastic laminæ (Fig. 2B). They were similar in structure to fœtal pulmonary arteries of corresponding diameter. Details of lumen-to-wall ratios are considered later in this paper. In the 4 patients, too, the small muscular arteries and arterioles showed no evidence of intimal proliferation, so that the histological changes corresponded to those of grade 1 hypertensive pulmonary vascular disease on the criteria of Heath and Edwards (1958). In the 2 remaining cases in group 1, that of an adult aged 31 years (case 6) and a child aged 5 years (case 4), the small muscular arteries and arterioles showed intimal fibrosis as well as the medial changes already described. These changes are of grade 3 severity based on the criteria already referred to (Table).

Among the patients of group 2, all of whom had free communication between the common ventricle and the pulmonary circulation, an infant aged 21 months (case 7) showed only grade 1 arterial change (medial hypertrophy), already described. The other 2 patients in the group showed intimal proliferation as well as medial change. In the boy aged 14 years (case 8) this intimal proliferation was cellular in nature, corresponding to grade 2 changes. In the boy aged 15 years (case 9), however, the changes in the pulmonary arteries were much more severe. The muscular pulmonary arteries and arterioles showed hypertensive pulmonary vascular disease of grade 4, which is usually associated with high pulmonary vascular resistance (Heath *et al.*, 1958a) and irreversible pulmonary hypertension (Heath *et al.*, 1958b). There was medial hypertrophy in the muscular arteries with the development of longitudinal and spirally arranged muscle just beneath the external elastic lamina. A distinct muscular media was found in pulmonary arterioles as small as 20 microns in diameter. Although there was no evidence of generalised dilatation in this case, complex " dilatation lesions " (Heath and Edwards, 1958) were present in the form of " plexiform lesions." These had the typical appearance of segmental dilatation of arterioles or of the smallest muscular arteries to form distended sacs, filled with proliferated cellular material in plexiform arrangement. Intimal proliferation was not severe in the small arteries and arterioles not included in the " dilatation lesions " and was mainly cellular. However, in a few muscular arteries in the lower lobes there was almost

total occlusion by fibro-elastic tissue and elastosis of the internal elastic lamina.

In the cases of group 3, all of which were in adults with acquired hypertension in the pulmonary arteries and veins, grade 3 changes were present. There was medial hypertrophy in arteries and arterioles and intimal fibrosis, as contrasted with cellular intimal proliferation (Fig. 2A).

The Degree of Medial Hypertrophy as Measured by the Lumen-to-Wall Ratio

In an attempt to estimate the degree of hypertrophy that was present, the lumen-to-wall ratios of 10 to 20 muscular arteries less than 300 microns in diameter in the upper and lower lobes were measured in 2 cases of each group. Cases 1 and 5 of group 1, cases 8 and 9 of group 2 and cases 10 and 11 of group 3 were studied. This method of investigation was not extended to include all patients in the series for the reasons stated below. For this study the method of Dammann and Ferencz (1956) was employed, but the thickness of the intima was not included in the measurements. The lumen-to-wall ratio was defined as the diameter of the lumen divided by twice the thickness of the media. In one of the group 2 cases (case 8) the sites of the lung from which the blocks had been taken were not known and hence an overall lumen-to-wall ratio for the case was calculated.

In some cases from groups 1 and 2 in which pulmonary venous hypertension had been present from birth, such as cases 1 and 9, the mediæ of the muscular arteries were uniformly thick throughout the lung and a comparatively small range of ratios was found in individual vessels. In case 1, for instance, the mean lumen-to-wall ratio of the muscular arteries in the upper and lower lobes was 1·5 and the range was 0·8 to 3·2. In case 9 the mean ratio for these vessels in the upper lobe was 1·5 and the range was 0·9 to 2·6, and in the lower lobe the mean ratio was 1·7 and the range 1·0 to 2·7. In case 5 from group 1, in which the media of the arteries in both upper and lower lobes was thinner than in cases 1 and 9 (the mean ratios in upper and lower lobes being 5·0 and 4·0 respectively), a wide range of ratios was found in the lower lobes (1·8 to 7·5). This suggests that while some arteries were hypertrophied others were dilated. In the adults in group 3 with acquired pulmonary venous hypertension the range of lumen-to-wall ratios was even greater, as is demonstrated by the findings in case 10 in which the mean lumen-to-wall ratio for the upper lobe was 7·0 and the range was 3·6 to 10·0; for the lower lobe the mean ratio was 10·4 and the range 5·7 to 15·0. The pulmonary arteries in these patients were the site of severe intimal fibrosis, and this change was most pronounced in the smallest arteries which also showed the most severe degree of thinning of the media.

It seems unsatisfactory to express different degrees of hypertrophy in some arteries and various stages of dilatation in others in the same case by a single number. The measurement of lumen-to-wall ratios is valueless if intimal fibrosis and vascular dilatation are present as in hypertensive pulmonary vascular disease of a severity equalling or exceeding grade 3, a state of affairs found in patients belonging to each of the three groups studied. In such cases the mean lumen-to-wall ratio lacks significance and, if the limitations of the

method are not appreciated, gives a false impression of the state of the media of the pulmonary arteries. The method seems to be valid only when early grades of hypertensive pulmonary vascular disease without dilatation are present.

The Distribution of Medial Hypertrophy in the Muscular Arteries throughout the Lung

One of the patients in group 3 with acquired pulmonary hypertension (case 13) is of particular interest in this connection as the mass of fibrous tissue in the mediastinum practically occluded the venous return through all the pulmonary veins except that from the right lower lobe. This vein was only partially occluded. Medial hypertrophy was found in the arteries and arterioles in all lobes, but was more severe in the lobes with severe venous obstruction.

Structural Changes associated with Pulmonary Venous Hypertension

These changes were considered to fall into four sub-groups: pulmonary congestion with hæmosiderosis, changes in the pulmonary veins, late changes in the lung substance and the presence of bone in the lung. These sub-groups are designated respectively by the letters "W," "X," "Y" and "Z" in the table.

Pulmonary Congestion with Hæmosiderosis (See Table 1). Distension of the capillaries in the alveolar walls and foci of hæmosiderin-laden macrophages occurred in every case (Fig. 3A) of all three groups, although they varied in severity in individual cases. Both were minimal in cases 1 and 5 (patients aged 7 months and 8 years respectively) and were severe in cases 2 and 9. In 1 of the patients with acquired pulmonary hypertension (case 10) both features were present only in the lower lobes.

Changes in the Pulmonary Veins (See Table 1). These changes were found in all but 3 patients in the series, the exceptions being 2 infants, 1 with a common ventricle (case 7) and 1 without (case 1), and a boy aged 8 years with congenital mitral incompetence due to a cleft in the anterior leaflet of the mitral valve (case 5, group 1). They were especially severe in a boy aged 15 years with mitral atresia and a common ventricle (case 9; Figs. 2C and 2D). The pulmonary veins more than 200 microns in diameter, identified by their position not in apposition to bronchi and by their connection with major, easily recognisable veins, were unusually thick-walled. The thick wall was composed of tightly packed, circularly arranged, smooth muscle fibres, sandwiched between prominent internal and external elastic laminæ. The appearance mimicked that of a muscular pulmonary artery (Figs. 2C and 2D). Internal to this media was a thick layer of cellular fibrous tissue which contained fusiform cells stained by the picric acid of Van Gieson's stain scattered between the collagen fibres (Figs. 2C and 2D). Most of the venules (100 microns in diameter) showed severe intimal fibrosis, acellular in most of them but cellular in a few. In 1 adult with acquired pulmonary hypertension (case 13) intimal fibrosis was severest in the veins and venules of lobes whose main veins were almost totally occluded by the mediastinal granuloma. There were no thrombi in the veins.

Of the three exceptions referred to previously the 2 infants had completely

normal veins and the 8-year-old boy (case 5) showed only minimal intimal fibrosis and a moderate increase in the muscle in the vein wall, which manifested as haphazardly arranged fibres in the media. In most cases the intimal fibrous tissue was cellular in the larger veins and acellular, even hyaline, in the venules, but in 1 adult with acquired pulmonary hypertension included in group 3 (case 12) the intimal reaction was extremely cellular, not only in the larger veins but also in the venules.

Late Changes in the Lung Substance (See Table 1). Extensive changes were found in the lung substance in representatives of all three groups. In the lower lobes the alveoli contained œdema coagulum, macrophages and erythrocytes, some of which had been ingested by phagocytes. Foci of hæmosiderin-containing macrophages were scattered extensively throughout the lung. Much of the œdema coagulum had been organised by cellular fibrous tissue so that the alveolar spaces contained collagen in many instances (Fig. 3B). The alveolar walls were grossly thickened; this was in part due to distension of alveolar capillaries and in part to widespread pulmonary interstitial fibrosis possibly due to organisation of œdema coagulum in the alveolar walls themselves. Similar changes were less severe or not found in the upper lobes. Many of the cells lining the alveoli had undergone metaplasia into cuboidal epithelium, and many of the intra-alveolar masses of fibrous tissue had become lined by endothelium. The appearances in the lower lobes were those classically referred to as " brown induration " (Fig. 3B). In 1 of the adults with acquired pulmonary hypertension (case 13) congestive changes were absent in the lobes with severe venous obstruction, but organising intra-alveolar exudate and pulmonary interstitial fibrosis were present in the only partially occluded right lower lobe. This type of change was not always present in so severe a form. In case 11, for instance, although macrophages, siderophages and pulmonary interstitial fibrosis were present, there was no evidence of intra-alveolar organisation of œdema coagulum. In other cases (case 6) severe changes were seen in focal areas only, the intermediate portions of lung showing only the arterial changes. It is likely that these areas were the result of old infarcts.

The Presence of Bone in the Lung (See Table 1). Spicules of bone were found in the lungs of 2 adults. One had had pulmonary venous hypertension from birth with no free communication between the systemic ventricle and the pulmonary circulation (case 6). The other (case 12) had acquired pulmonary hypertension (Fig. 3C). The extensive changes in the pulmonary substance described in the previous paragraph were present in both.

Comment

It is now well established that chronic pulmonary venous hypertension is associated with a raised blood pressure in the pulmonary arteries. Catheterisation studies have demonstrated this association in mitral stenosis (Dexter *et al.*, 1950), left ventricular failure (Dexter *et al.*, 1950), myxoma of the left atrium (Van Buchem and Eerland, 1957), myocardial fibrosis (Heath *et al.*, 1957) and granuloma of the mediastinum pressing on pulmonary veins

(Edwards and Burchell, 1951). When the pulmonary venous hypertension is acquired in adult life, as in the examples cited and in the cases of group 3 in the present series, so is the hypertension in the pulmonary arteries. When pulmonary venous hypertension is present from birth, as in the cases of groups 1 and 2, so is the pulmonary arterial hypertension. Hence, in the lung of the patient with chronic pulmonary venous hypertension, in addition to the effects of hypertension on the pulmonary veins and capillaries, the latter leading to structural effects in the lung substance, there are also the effects of hypertension on the pulmonary trunk and the small pulmonary arteries.

This investigation showed that when pulmonary venous hypertension is present from birth, as in the cases included in groups 1 and 2, no matter whether the associated pulmonary arterial hypertension is due to the raised blood pressure in the pulmonary veins alone or is associated with the presence of a free communication between a common ventricle and the pulmonary circulation, the configuration of the elastic tissue of the pulmonary trunk is of fœtal type, and resembles that of the adult aorta. This is because the presence of pulmonary arterial hypertension from birth always leads to the retention of the fœtal, aorta-like configuration of elastic tissue in the pulmonary trunk (Heath *et al.*, 1958d), presumably provided such hypertension exceeds a certain critical level. Conversely, the finding of an adult pulmonary configuration of elastic tissue in the pulmonary trunk in the cases of group 3 is related to the acquired pulmonary arterial hypertension which follows acquired pulmonary venous hypertension. In these cases, as has been demonstrated in atrial septal defect and mitral stenosis (Heath *et al.*, 1958d), the normal transition from a fœtal or aortic to an adult pulmonary configuration of elastic tissue occurs long before the onset of hypertension in the pulmonary arteries.

In the group 1 cases in which anatomical obstruction to pulmonary venous return was not associated with a septal defect, the structural changes in the pulmonary arteries were those of the earliest stages of hypertensive pulmonary vascular disease, being grade 1 in 4 cases (Fig. 2B), and grade 3 in the other 2. This indicates that, as a result of the elevated blood pressure in the pulmonary veins, the thick-walled characteristics of fœtal pulmonary arteries are retained with a persistence of arterial hypertension in the lung from fœtal to post-natal life. To this may be added non-specific obstructive lesions without arterial dilatation. However, the progression of any additional structural changes in the pulmonary arteries including dilatation occurred to any appreciable degree only in one of the cases of group 2 in which there was a free communication between a common ventricle and the pulmonary trunk. This is in accord with our previous observation (Heath and Edwards, 1958) that pulmonary hypertension associated with congenital cardiac septal defects, probably because of its duration and magnitude, predisposes to the severer grades of hypertensive pulmonary vascular disease (grades 4 to 6), whereas chronic rheumatic mitral stenosis usually leads to only grade 3 structural changes. The development of grade 4 changes in one of the patients with anatomical pulmonary venous obstruction associated with a free communication between the systemic ventricle and the lesser circulation demonstrates that the presence

of pulmonary venous hypertension does not prevent the development of the higher grades of structural change in the pulmonary arteries. In the cases of acquired pulmonary hypertension (group 3), non-specific severe intimal fibrosis (grade 3) was the most characteristic feature associated with medial hypertrophy (Fig. 2A).

Pulmonary veins also show progressive structural changes when the blood pressure in them is elevated (Figs. 2C and 2D). The small venules and capillaries are distended, and there is diapedesis of erythrocytes into the alveolar spaces where they are ingested by macrophages to form foci of pulmonary hæmosiderosis (Fig. 3A). Veins, like arteries, exhibit medial hypertrophy and intimal fibrosis as a reaction to an elevation in their intraluminal pressure (Figs. 2C and 2D). When the pulmonary venous hypertension is severe, as appeared to be the case in this series, the muscle in the vein wall, which is usually arranged in an irregular fashion intermingled with collagenous and elastic fibrils, undergoes a remarkable change. The muscle becomes condensed into a distinct muscular media devoid of collagen and fragmented elastic fibrils and is sandwiched between internal and external elastic laminæ, so that in some instances the appearance of an arterial media is simulated (Figs. 2C and 2D). This illustrates the general tendency for adaptation on the part of vascular structures exposed to an abnormal blood pressure.

Hence, pulmonary veins with an intraluminal blood pressure of about 35 mm. Hg have certain structural features of the normal muscular pulmonary artery, and pulmonary arteries subjected to an increased mean blood pressure around 70 mm. Hg look like systemic arteries. The pulmonary trunk exposed to a blood pressure approaching systemic magnitude from birth is as thick as, and has an elastic tissue configuration like, the aorta. Severe intimal fibrosis is as characteristic of veins subjected to hypertension as it is of pulmonary arteries subjected to an elevated blood pressure. Furthermore, the present study shows that in pulmonary veins, as in the arteries in hypertensive pulmonary vascular disease, the intimal fibrosis increases in severity with increasing age of the patient and increasing duration of hypertension.

The hypertrophy and condensation of smooth muscle in the walls of the pulmonary veins is pathognomonic of pulmonary venous hypertension, but the changes in the intima of veins and in the lung substance, while characteristic of raised pressure in the pulmonary veins and capillaries, are in no sense specific. Severe intimal fibrosis in pulmonary veins is commonly found in disease associated with high pulmonary blood flow, such as atrial septal defect (Heath and Edwards, 1958).

The changes in the lung substance, such as pulmonary hæmosiderosis (Fig. 3A) and the presence of œdema coagulum with its subsequent fibrosis in the alveolar walls and spaces (Fig. 3B), depend in the present series on the distension of the pulmonary capillaries by pulmonary venous hypertension and the resulting diapedesis of red cells and exudation of œdema fluid into the lung substance. However, similar changes are found in the absence of pulmonary venous hypertension. All the histological components of " brown induration " can be produced focally by old pulmonary infarcts. When changes of this

nature are found focally, their cause should be interpreted with caution, for, even in the presence of proved pulmonary venous hypertension, they may be due to old pulmonary infarcts.

The exudation of fluid from the pulmonary capillaries in diseases associated with pulmonary venous hypertension leads to œdema coagulum and its subsequent organisation in both the alveolar space and walls (Fig. 3B). The nature and site of the fibrous tissue depend on the severity and chronicity of the pulmonary œdema. When this is severe and acute, as in pneumonia, rupture of an aortic aneurysm into the pulmonary artery or, theoretically, a sudden elevation in pulmonary venous blood pressure, organisation of the œdema coagulum may take place in the alveolar spaces and the fibrous tissue is cellular. This is seen in organising pneumonia and was reported in a case of rupture of an aortic aneurysm into the pulmonary trunk (Heath *et al.*, 1958c). However, since pulmonary venous hypertension is usually chronic, it is common for the coagulum to collect and be organised in the alveolar walls as a result of " chronic " pulmonary œdema due to repeated subclinical attacks of pulmonary œdema as in mitral stenosis, myxoma or thrombus of the left atrium occluding pulmonary veins, congenital stenosis of the pulmonary veins or mediastinal granulomata interfering with pulmonary venous return. In such diseases pulmonary interstitial fibrosis develops (Andrews, 1957), and since they are associated with prolonged pulmonary œdema, the fibrous tissue becomes old and acellular. This is in contrast to the cellular fibroblastic reaction in the alveolar spaces which follows acute pulmonary œdema, due, let us say, to a sudden elevation of pulmonary venous hypertension.

Spicules of bone in the lung, found in 2 adults in the present series, are sometimes associated with pulmonary hypertension (Fig. 3C). Rarely, they occur in the alveolar spaces in association with pulmonary arterial hypertension and normal blood pressure in the pulmonary capillaries as in a case of gonadal dysgenesis that one of us (D.H.) studied recently. More commonly, however, there is hypertension in both pulmonary arteries and veins in such cases. For this reason bone in the alveolar spaces is most frequently found in mitral stenosis (Hicks, 1953; Whitaker *et al.*, 1955).

Summary

A description is given of the histological changes found in the pulmonary arteries, veins and parenchyma of 13 patients with diseases associated with pulmonary venous hypertension. The cases were considered in three groups. The first group comprised 6 patients who had anatomical malformation of the heart leading to pulmonary venous hypertension from birth; none of them had cardiac septal defects so that the associated pulmonary arterial hypertension was related solely to the elevated blood pressure in the pulmonary veins. The second group consisted of 3 patients who had mitral atresia and a common ventricle, so that the pulmonary arterial hypertension was primarily due to a direct communication between the systemic ventricle and the lesser circulation. The third group consisted of 4 patients with heart disease leading to acquired pulmonary venous hypertension.

The configuration of elastic tissue in the pulmonary trunk is of fœtal, aortic type when the hypertension in the pulmonary arteries and veins is present from birth. It is of the adult pulmonary type when the elevation of blood pressure in the pulmonary artery is acquired in adult life.

The small pulmonary arteries show various grades of hypertensive pulmonary vascular disease.

The pulmonary veins are thick-walled owing to increase in muscle tissue in the media and to intimal fibrosis. The formation of a distinct compact muscular media with internal and external laminæ in the wall of the vein is pathognomonic of pulmonary venous hypertension. The characteristic severe intimal fibrosis in the vein may be cellular or acellular; it is more pronounced in the adult with acquired pulmonary venous hypertension than in the child with congenital pulmonary venous hypertension.

In the lung substance, the earliest sign of pulmonary venous hypertension is capillary distension with pulmonary hæmosiderosis. Later severe changes occur. These are the formation and subsequent organisation of œdema coagulum in the alveolar spaces and walls. Finally, the affected lung is solid with intra-alveolar fibrosis, chronic pulmonary interstitial fibrosis, and packing of the air spaces with macrophages, many of which contain hæmosiderin.

Spicules of bone form in the alveolar spaces infrequently. The changes in the lung substance are characteristic of, but not pathognomonic of, pulmonary venous hypertension since they occur in other conditions, including pulmonary infarction.

REFERENCES

Andrews, E. C., Jr. (1957): *Bull. Johns Hopkins Hosp.*, **100,** 28.

Becker, D. L., Burchell, H. B., and Edwards, J. E. (1951): *Circulation,* **3,** 230.

Dammann, J. F., Jr., and Ferencz, Charlotte (1956): *Amer. Heart J.*, **52,** 7.

Dexter, L., Dow, J. W., Haynes, F. W., Whittenberger, J. L., Ferris, B. G., Goodale, W. T., and Hellems, H. K. (1950): *J. Clin. Invest.*, **29,** 602.

Edwards, J. E., and Burchell, H. B. (1951): *Amer. med. Ass. Arch. Int. Med.*, **87,** 372.

Heath, D., and Best, P. V. (1958): *J. Path. Bact.*, **76,** 165.

Heath, D., Cox, E. V., and Harris-Jones, J. N. (1957): *Thorax,* **12,** 321.

Heath, D., and Edwards, J. E. (1958): *Circulation.* (In press.)

Heath, D., Helmholz, H. F., Jr., Burchell, H. B., Dushane, J. W., and Edwards, J. E. (1958a): *Circulation.* (In press.)

Heath, D., Helmholz, H. F., Jr., Burchell, H. B., Dushane, J. W., Kirklin, J. W., and Edwards, J. E. (1958b): *Circulation.* (In press.)

Heath, D., Parker, R. L., and Edwards, J. E. (1958c): *Brit. J. clin. Pract.* (In press.)

Heath, D., Wood, E. H., Dushane, J. W., and Edwards, J. E. (1958d): *J. Path. Bact.* (In press.)

Hicks, J. D. (1953): *J. Path. Bact.*, **65,** 333.

Larrap W. F., Parker, R. L., and Edwards, J. E. (1949): *Proc. Staff Meet., Mayo Clin.*, **24,** 31

Parker, L., Jr., and Weiss, S. (1936): *Amer. J. Path.*, **12,** 573.

Van Buchem, F. S. P., and Eerland, L. D. (1957): *Dis. Chest,* **31,** 61.

Whitaker, W., Black, A., and Warrack, A. J. N. (1955): *J. Fac. Radiol.*, **7,** 29.

Brit. J. Dis. Chest (1959) **53**, 19

SEGMENTAL PULMONARY ARTERY ANEURYSMS WITH PERIPHERAL VENOUS THROMBOSIS

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Pulmonary arterial aneurysms are not common and have been classified by Brenner (1935) into four groups: mycotic, congenital, syphilitic and traumatic.

The infecting source of the mycotic aneurysms is usually obvious (Stengel and Wolferth, 1923; Brenner, 1935). It is, however, probable that infected pulmonary emboli or secondarily infected infarcts produce pulmonary abscesses (Davison, 1958) more often than aneurysms. In a few cases, such as those reported by Fowler (1933), Carroll (1950), and Boucher, Protar and Bertein (1951), pulmonary embolus from infected thrombus resulted neither in aneurysm nor abscess formation.

In Brenner's ten congenital cases the main pulmonary artery was affected and in six this was associated with probable pulmonary hypertension due to congenital cardiac lesions. In one case the elastic was deficient.

Syphilitic and traumatic aneurysms need not be mentioned further as they are not relevant to the cases to be discussed. Nor will Rasmussen aneurysms affecting the small pulmonary arteries be considered.

Since Brenner's paper, fusiform dilatation of the main pulmonary arteries, associated with pulmonary hypertension, has been recognised (Evans, Short and Bedford, 1957). In many cases the pulmonary hypertension resulted from pulmonary thrombo-embolism. Space does not permit these to be reviewed, but in none has a saccular aneurysm been reported. The patient with pulmonary hypertension reported by Mackenzie and Clagett (1953) had a fusiform dilatation apparently restricted to the left upper lobe artery.

Aneurysms resulting from non-infected thrombotic embolus were thought by Stengel and Wolferth (1923) not to occur. Hall (1957), however, states that, though rare, they may occur and are then usually associated with circulating calcific particles of undisclosed ætiology. It is possible that the occasional aneurysms produced by Muirhead and Montgomery (1951) were due to chance infection of their emboli.

Thrombophlebitis may be the presenting feature of Buerger's disease, but the arterial involvement is almost always systemic and never produces aneurysms.

We report here two unusual cases of aneurysm of the segmental pulmonary arteries, of which one was briefly described by Russell in 19[illegible]. A search of the literature revealed only two other cases, those of Beattie and Hall (1911) and

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of Pirani, Ewart and Wilson (1949), where the aneurysms were thought to be mycotic, although in neither case was an infecting organism nor its source demonstrated. (Table I.)

TABLE I.—SUMMARY OF THE FOUR RECORDED CASES

	Age and sex	*Duration of history*	*Fever*	*Cerebral complication*	*Systemic artery involvement*	*Condition of lungs*	*Heart*
Beattie and Hall (1911)	M. 21	6/12	+	Neg.	Neg.	Aneurysm of arteries to: left lung right middle lobe right upper lobe	Mural thrombus right ventricle
Pirani *et al.* (1949)	M. 14	4 yrs.	+	+	Neg.	Aneurysms of arteries to: right upper lobe right lower lobe left lower lobe	Mural thrombus in slightly hypertrophied right ventricle
Hughes and Stovin (1958): Case 1	M. 35	4 yrs.	+	+	Neg.	Aneurysm of arteries to: right middle lobe right lower lobe left lower lobe. Obliteration of left lower lobe	Little endocardial fibrosis in contracted right ventricle
Case 2	M. 14	3½ yrs.	+	+	? ±	Aneurysms of: left basal artery right main artery. Cord like other arteries	Thrombus in right atrium and ventricle

The purpose of this paper is to draw attention to the clinical picture presented by these four cases and to suggest that their rarity may be due to the concurrence of two independent causes.

CASE 1. F.W., aged 35, began in May 1953 to get recurrent venous thromboses affecting both legs, for one of which he was admitted to hospital. The sedimentation rate was 66 mm./1 hour, but all other investigations, including chest X-ray, blood culture and blood W.R., were normal. Treatment with antibiotics produced no definite improvement.

In October 1953 he was admitted to the London Hospital complaining of headaches, vomiting and blurring of vision in the left eye. Examination of the central nervous system showed that he was slightly drowsy but orientated, with minimal photophobia and neck stiffness; there was bilateral papilloedema, left more than right, but no other localising signs. Apart from the raised pressure

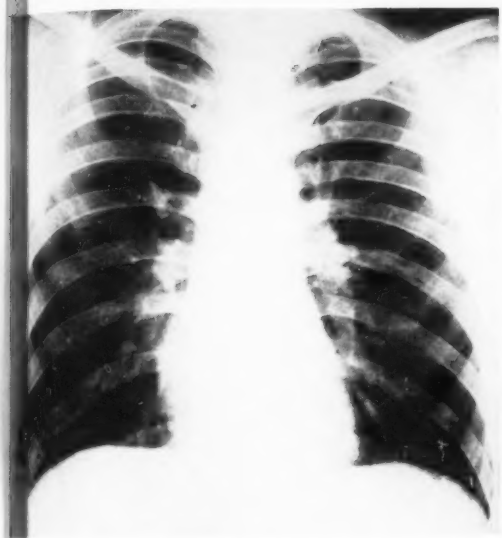

FIG. 1.—Case 1. X-ray of the chest of November 1953.

FIG. 2.—Case 1. X-ray of the chest of September 1955 showing rounded shadow in the right lower hilum with normal lung markings peripherally.

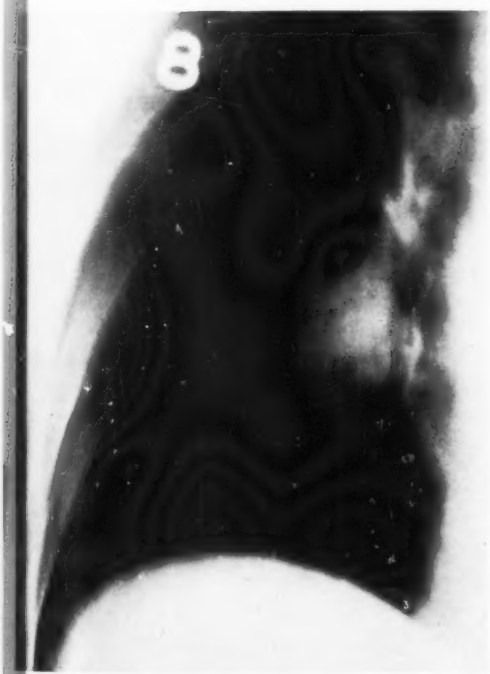

FIG. 3.—Case 1. Lateral tomogram showing the solid nature of the shadow seen in Fig. 2.

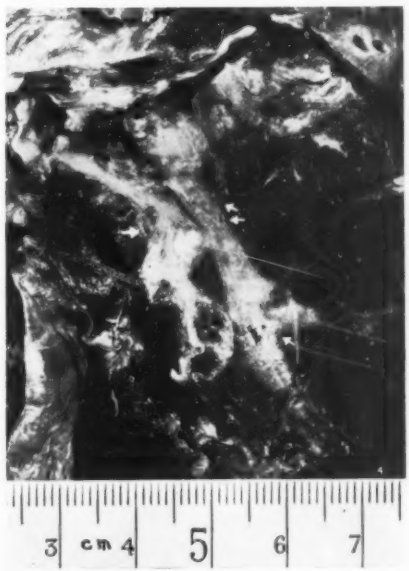

FIG. 4.—Case 1. Left lower lobe. The apical segmental artery runs across the top and a cut has been made into the aneurysm. Enlarged bronchial arteries are indicated in the fibrotic adventitia of the occluded basal segmental artery.

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FIG. 5.—Case 1. The site of rupture of the aneurysm. There is a cellular infiltrate in the thrombus in the pulmonary artery (left-hand border) and in the aneurysm (top). This infiltrate extends into the adventitia. Arrows indicate abnormal bronchial arteries. Hart's elastic and van Gieson (× 17).

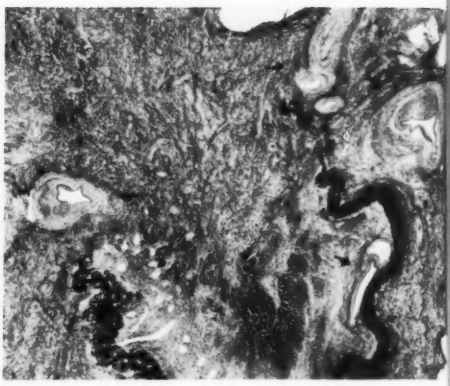

FIG. 6.—Case 1. Disruption of the elastic of the l lateral basal artery with fibrosis of the lumen a adventitia. Arrows indicate the abnormal bronchi arteries. Hart's elastic and van Gieson (× 16).

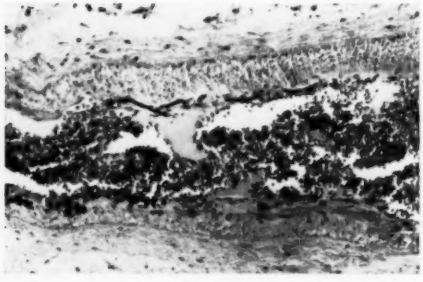

FIG. 7.—Case 1. Left hilar bronchial artery showing mineral impregnation of the internal elastic lamina. Haematoxylin and eosin (× 115).

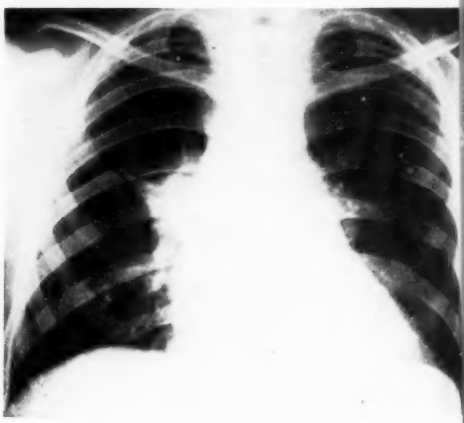

FIG. 8.—Case 2. X-ray of the chest showing right h shadow. Film taken three weeks before deat

the C.S.F. was normal. Examination of the blood showed a sedimentation rate of 68 mm./1 hour, but no abnormality in red or white cells, hæmoglobin or bleeding time. Clinically, radiologically and electrocardiographically the respiratory and cardiovascular systems were normal (Fig. 1). The liver and spleen were not enlarged.

A right internal jugular venous thrombosis appeared which suggested the diagnosis of cerebral venous sinus thrombosis. On November 11, 1953, a right sub-temporal decompression was performed to preserve vision. After this he slowly improved. Anti-coagulant therapy (phenylindandione) was started and the patient discharged.

During the ensuing two years venous thromboses recurred despite continued anti-coagulant therapy. At one out-patient attendance in 1954 he complained of attacks of shivering; when examined he was apyrexial, but dilated veins in which the blood flowed upwards were seen on the abdominal wall. There was no œdema.

A routine chest X-ray in September 1955 (Fig. 2) showed a rounded mass in the right lower lobe. He was readmitted; no abnormal physical signs were found, and there was no clinical evidence of pulmonary hypertension. Tomograms were suggestive of a neoplasm arising from the basal bronchi of the right lower lobe (Fig. 3). No definite change could be seen in the lung field peripheral to this mass and bronchoscopy was normal. On November 18, 1955, a right middle and lower lobectomy was undertaken.

The surgical specimen showed an aneurysm filled with grey-brown thrombus (3×2 cm. diam.) situated on the main basal segmental artery. A second similar aneurysm (1 cm. diam.) was present in the hilum of the middle lobe. The arteries distal to the aneurysm appeared macroscopically normal. The microscopy will be described later.

The patient remained perfectly well, without anti-coagulants, until he suddenly "vomited" a large amount of blood on April 25, 1957. He was admitted to hospital and transfused to good effect; some rhonchi only were noticed in his chest and a chest X-ray showed the signs of his operation only. In view of the dilated abdominal veins it was thought that he had bled from œsophageal varices. He was transferred to the London Hospital on May 8, 1957. On admission he felt and looked well and had no fever; in the abdomen the liver and spleen were not felt nor was there an ascites, one dilated vein was detected on the abdominal wall but this was less prominent than in 1954; the respiratory and cardiovascular systems were normal. Five minutes after examination he died from a copious hæmoptysis.

Pathology. (1) *Macroscopic*

The body at autopsy was not wasted and showed scars of his previous operations. Death was due to inhalation of blood. A saccular aneurysm (1·5 cm. diam.) in the subapical segmental artery of the left lower lobe had perforated into the adjacent bronchus. The whole length (2·3 cm.) of this artery from its origin to the aneurysm was diffusely dilated and partially occluded by old white thrombus and the wall contained flecks of atheroma (Fig. 4). The main basal segmental artery, its branches to the lower lobe and several arteries of both upper lobes were occluded by organised white thrombus which had recanalised peripherally. Old fibrotic and more recent infarcts were present in the right upper lobe. All the thrombosed arteries showed a broad zone of

adventitial fibrosis in which enlarged bronchial arteries could be discerned. The main right and left pulmonary arteries were normal.

There was fibrous obliteration with recanalisation of the lumen of the inferior vena cava extending inferiorly from a point 1·5 cm. above the origin of the left renal vein to both femoral veins. The lower level of the obliteration was not determined and the upper level appeared smooth. Similar changes were seen in both lateral cerebral venous sinuses and extending slightly into the right internal jugular vein. The abdominal and portal veins were dilated.

The heart was flabby and pale (10 oz., 284 G.). The contracted right ventricle (0·6 cm. thick) had a few small patches of endocardial fibrosis; the chambers and valves were normal.

The brain showed cortical atrophy and gliosis with localised hydrocephalus beneath the decompression, but was otherwise normal.

The other organs showed no abnormality.

(2) *Microscopic*

Microscopically the changes in the lungs may be considered under three headings.

(*a*) *Elastic Pulmonary Arteries*

The main right and left pulmonary arteries were normal. In the wall of each aneurysm the elastic and muscle fibres were destroyed in segments. In these segments the media was heavily infiltrated with foam cells, plasma cells and lymphocytes and this infiltrate extended both into the overlying thrombus and into the adventitia (Fig. 5). In the occluded non-aneurysmal left lower lobe artery the elastica in a large segment of the wall had been replaced by fibrous tissue which blended with the fibrous tissue of the occluded lumen and of the adventitia (Fig. 6). In this region and in parts of the right lower lobe adjacent to the aneurysm the lumina of these occluded arteries had been recanalised by ingrowths of enlarged abnormal bronchial arteries (see below).

(*b*) *Muscular and Small Elastic Pulmonary Arteries*

In all lobes these arteries showed concentric or eccentric fibrous and elastic tissue sclerosis of the intima, with slight hyperplasia of the medial muscle and elastic fibres. There were no segmental changes indicative of polyarteritis nodosa, and these changes were thought to be secondary to the proximal thrombosis.

(*c*) *Bronchial Arteries*

At the hilum of the left lung several of the larger arteries showed thickening of the muscle of the media and fragmentation with calcium and iron impregnation of the internal elastic lamina (Fig. 7). Several of these hilar vessels also had a fibroblastic intimal thickening unrelated to the mineral impregnated elastic. In the lung, especially in the region of the thrombosed pulmonary arteries, the bronchial arteries were greatly altered; a complete loss of the elastic lamellæ was accompanied by thinning of the media, the residual fibres of which appeared poorly stained and separated by œdema, and frequently the lumen was narrowed or distorted by conspicuous cushions of œdematous sparsely cellular tissue. The subpleural and septal bronchial arteries showed similar but less

marked œdema, fibrosis, and loss of muscle and elastic fibres. None of the bronchial arteries showed any inflammatory cellular infiltration, nor were any "sperrarterien" (Verloop, 1948) found.

The pulmonary veins showed fibrosis and muscular thickening of their media.

The systemic veins showed organised and recanalised thrombus in their lumina with slight fibrosis and muscular hypertrophy of their media, without any destruction of elastic tissue and without adventitial fibrosis or any cellular infiltration. Recanalised thrombus was present in the dural sinuses. In the kidneys, besides changes due to renal vein thrombosis, an occasional glomerulus showed focal fibrosis with capsular fibrosis and a periglomerular round cell infiltration.

No significant changes were seen elsewhere.

CASE 2. B.S., male, aged 11½, developed normally apart from an occult spina bifida until July 1950, when he had an injury to his left forehead, and a week later a further injury to his jaw which became inflamed.

On August 30, 1950, he was admitted to the London Hospital with left otitis media, papillœdema and raised lumbar C.S.F. pressure. He had an exploration of his left mastoid which was proved to be clear; thrombosis of the sagittal sinus was then suspected. A right sub-temporal decompression relieved the raised intracranial pressure. His progress was marred by an irregular pyrexia to 102° F., the development of a false aneurysm of the left carotid artery at the site of an angiogram, and a left brachial thrombophlebitis extending into the jugular vein with a left lower lobe pulmonary infarction. The spleen was not enlarged. Blood culture and urine were sterile, Widal and Weil-Felix agglutinations were negative. He became apyrexial following ligation of the false aneurysm, the contents of which were sterile.

During the ensuing year and a half he remained well except for short bouts of headache and vomiting.

In October 1952 he had shivering bouts for two weeks and was re-admitted with thrombosis of the right internal jugular vein causing superficial venous engorgement over both sides of the neck, shoulders, upper arms and upper chest. The blood flowed downwards in these vessels. A right calf vein thrombosis occurred and three days later a pulsating swelling was noted in the right gastrocnemius. The posterior tibial artery was ligated with control of the aneurysm. During this admission he had irregular bouts of fever up to 104·8° F., but these were latterly controlled by cortisone. Chest X-ray and electrocardiogram were normal and examination of the blood showed a persistent anæmia and a fluctuating neutrophil leucocytosis. Blood culture was again sterile.

In February 1953 he developed superficial chest vein thrombosis. He was again admitted because of the development of a right conjunctivitis and an irregular pyrexia with rigors which settled when cortisone was restarted. At this time the plasma proteins were normal and no L.E. cells were seen in the blood. He was discharged, continuing to take cortisone.

Two months later he developed rigors and painful nodules over the left tenth and twelfth ribs. He was cyanosed on exertion. All these signs regressed on admission.

During the next three months he had two hæmoptyses and became more breathless and cyanosed on exertion. On October 21, 1953, he was re-admitted

with further hæmoptyses and fever. Distended superficial veins were now visible over the abdomen, and though the heart was not enlarged he developed a systolic murmur in the pulmonary area, at first associated with weekly bouts of fever, but later becoming constant. A further blood culture was sterile. Chest X-ray showed some consolidation of the right upper lobe with apparently enlarged right hilar lymph glands (Fig. 8). An electrocardiogram was normal. Seventeen days later (December 24, 1953) a further large hæmoptysis terminated his life.

Pathology

At autopsy the boy was well nourished. The heart (9½ oz., 270 G.) had a thickened pericardium but there was no right ventricular hypertrophy (0·4 cm. thick). Organised thrombus was present in the right auricle and extended down through the tricuspid valve into the ventricle. The valves were normal. The left common carotid artery was occluded and a little adherent thrombus projected into the lumen of the adjacent jugular vein. Organised and recanalised thrombus was present in both lateral sinuses and posteriorly in the superior sagittal sinus.

A saccular aneurysm (1·5 cm. diam.), partly filled with laminated thrombus, projected from the right main pulmonary artery. The arteries to the right upper and lower lobes were cordlike and obliterated by old white thrombus. A saccular aneurysm (1·7 cm. diam.) on the left anterior basal segmental artery had ruptured into a bronchus. The artery distal to this aneurysm appeared normal. The posterior basal artery distal to another aneurysm was obliterated. Adherent thrombus was present in two upper lobe segmental arteries. The other organs showed changes of congestive heart failure only. Neither the ligated carotid aneurysm nor the aneurysm in the right leg could be defined at post-mortem. The cerebral pathology has been described by Russell (1954).

The histology of the pulmonary artery aneurysms, the bronchial arteries, and of the peripheral pulmonary arteries was closely similar to the changes described for the first case. There was no evidence of infection, of systemic arterial disease, nor of focal glomerular fibrosis.

Comment

The chief features of our two cases and of those reported by Beattie and Hall (1911) and Pirani *et al.* (1949) are shown in Table I.

The age of these four male patients varied from 14 to 35 years: the illness of Beattie and Hall's case lasted six months, the duration of the illness in the other three cases was from three and a half to four years.

Except for Beattie and Hall's case, signs of raised intracranial pressure due to jugular or lateral sinus thrombosis were a prominent feature of the early stage. In case 2 and in the case of Pirani *et al.* it was the presenting feature, but in case 1 there had been a prior episode of thrombosis in the right saphenous vein. Pirani *et al.* were unable to account for the recurrent headache and raised intracranial pressure, though they tentatively postulated an encephalitis. However, they did consider that the cerebral episode might have been an "otitic" hydrocephalus consequent upon a thrombosis of the jugular veins,

which were not examined at autopsy. The reason they gave for rejecting this was that the dural and meningeal vessels were normal. In our two cases the meningeal vessels were normal in spite of dural sinus thrombosis, and the jugular veins, which clinically had been thrombosed, were at post-mortem recanalised with single lumina. In view of these observations and of the very close similarity of clinical history between the case of Pirani and our case 2, we consider that the former case presented with an "otitic" hydrocephalus following a jugular venous thrombosis.

With minor variants the next phase in the illness is one of recurrent thromboses of superficial and deep veins. In all but case 2 there was never at any time any evidence of peripheral arterial disease. However, in case 2 there occurred two aneurysms, the first directly related to trauma (carotid arteriography), and the second of undetermined ætiology in the right calf. Neither aneurysm was identified at post-mortem nor did the systemic arteries show any evidence of a primary arterial disease histologically.

This stage was also characterised by febrile episodes which appeared to be related to the thrombotic incidents. It is important to note that no case showed concrete clinical or pathological evidence of septicæmia. In our two cases and in the case of Pirani *et al.* blood cultures were repeatedly negative, and in Beattie and Hall's case no organisms could be demonstrated at post-mortem. There was no splenomegaly and the intra-cardiac thrombi appeared to be terminal. Pirani suggested that the organisms responsible were of such a low grade of virulence as to be confined to the leg vein thrombus and any emboli from this thrombus. Such an hypothesis is difficult to refute without adequate bacteriological studies, but the thrombosed veins in our two cases showed no evidence of destruction of their elastic tissue nor sclerosis of their adventitia which would indicate a thrombophlebitis rather than a phlebothrombosis. Further, the pyrexia in both of our two cases failed to respond to antibiotics.

In the third stage of the illness attention is usually drawn to the chest because of hæmoptysis. Case 1 developed an opacity in his right lung which resembled a neoplasm sufficiently closely for thoracotomy to be advised, as it is known that recurrent thrombophlebitis may be associated with a carcinoma. Similarly the radiological picture in the case of Pirani *et al.* was interpreted as secondary neoplasm and deep X-ray therapy was given. The X-ray appearances in case 2 were interpreted as enlarged hilar lymph nodes. No X-ray examination was made in the case of Beattie and Hall. The hæmoptyses continue for several weeks until a fatal rupture of a pulmonary aneurysm.

Diagnosis

With a known history of venous thromboses the possibility of progressive thrombo-embolic occlusion of the pulmonary circulation must be seriously considered as hæmoptyses are common in this condition. However, the bleeding is not usually so severe and is almost always accompanied by progressive dyspnœa and cyanosis and often there is evidence of pulmonary hypertension. These symptoms were absent in three and only mild in the fourth of the cases

we have reviewed, and at no stage did our two cases show electrocardiographic right ventricular strain or hypertrophy.

The radiological diagnosis of aneurysms of the segmental pulmonary arteries is difficult and it is noteworthy that in two of these four cases the lung opacities were taken to be neoplastic, while in case 2 and by Pirani they were interpreted as enlarged hilar nodes. Barnes and Stedem (1933) described a further case, not associated with peripheral venous thromboses, in which again the aneurysms were thought to be neoplastic. These authors suggested that a definite vascular connection with the hilum should be sought, although this could be difficult if the aneurysm were very near to the hilum. It is not always easy to decide if the pulsation seen on screening is expansile or transmitted. Even the latter does not exclude an aneurysm as it may well be partly filled with thrombus. Angiograms were not used in any of these cases.

Pathology

Though unlikely, we cannot exclude an infection by some organism, of low-grade virulence, not detectable by the usual cultural, serological or staining techniques, and not affected by antibiotics or adrenal cortical steroids. However, there is a greater degree of inflammatory cellular infiltration in the wall of the pulmonary artery aneurysms than is seen in the organisation of a simple thrombus, although this need not necessarily indicate a bacterial cause. The focal glomerular scars in the kidneys of case 1 might indicate a past subacute bacterial endocarditis, but there was no other post-mortem evidence for this. These scars may be found in other conditions such as polyarteritis nodosa and sulphonamide hypersensitivity (Allen, 1951). Neither of our cases had any of the clinical hæmatological or pathological lesions of polyarteritis with lung involvement described by Ellman (1956) and Rose and Spencer (1957).

The changes in the bronchial arteries associated with pulmonary arterial occlusion or with pulmonary hypertension are similar, consisting of muscular hypertrophy with splitting of the elastic lamina (Ellis, Grindlay and Edwards, 1952; Evans and others, 1957). The changes in the bronchial arteries in our cases were entirely different and were degenerative. Unfortunately Beattie and Hall and Pirani did not describe the bronchial arteries, though the vessel shown in Pirani's figure 5 might be a bronchial artery similar to those in our cases.

In the absence of any other definite pathology we feel that in our cases the bronchial arteries show evidence of a qualitative defect leading to degeneration with mineral impregnation of the elastica interna and fibrous tissue replacement of the muscle and elastic coats. This defect is probably congenital in view of the abnormality being confined to the bronchial arterial system and in view of the early age of two of the four cases. Though there is extensive loss of the elastic tissue in the occluded and aneurysmal pulmonary arteries this is directly related to present and past organisation of thrombus and is less diffuse than in the bronchial arteries. However, this does not exclude the elastic tissue of the pulmonary arteries being also qualitatively defective.

Verloop (1948) has shown the structure of the bronchial arteries to be

different from normal systemic muscular arteries in that intimal longitudinal muscle fibres are developed. It is, therefore, possible that their elastic tissue may differ from that elsewhere in the body.

It is postulated that these degenerative changes in the bronchial arteries result in an inadequate nutrition to the pulmonary arteries so that an embolus is organised in a different fashion from that occurring in a normal pulmonary artery. This results in a cellular inflammatory reaction, destruction of the elastic tissue, and aneurysm formation.

We consider that two factors have operated in the production of the aneurysms in our cases, namely bronchial artery degeneration and pulmonary artery embolism. We differ from D'Aunoy and von Haam (1934), who suggested that the factors were damage to the vessel wall and increased pulmonary arterial pressure.

The occurrence of cerebral venous sinus thrombosis in our cases remains unexplained, as does the ætiology of the thrombophlebitis migrans.

Summary

Two cases in which pulmonary artery aneurysms and peripheral venous thromboses coexisted are described in detail, and similar cases in the literature are reviewed.

The clinical course of these cases is outlined and divided into three phases, those of " otitic " hydrocephalus, peripheral venous thrombosis and pulmonary artery aneurysm formation. The pathological description is given and it is suggested that the pulmonary artery aneurysms may be related to a qualitative defect, possibly congenital, in the bronchial arteries.

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REFERENCES

ALLEN, A. C. (1951): " The Kidney." London: Churchill.
BARNES, J. M., and STEDEM, D. E. (1933): *Amer. J. Roentgenol.*, **30**, 443.
BEATTIE, J. M., and HALL, A. J. (1911-12): *Proc. R. Soc. Med.*, **5** (iii), 147.
BOUCHER, H., PROTAR, M., and BERTEIN, J. (1951): *Ann. Méd.*, **52**, 803.
BRENNER, O. (1935): *Arch. intern. Med.*, **56**, 1189.
CARROLL, D. (1950): *Amer. J. Med.*, **9**, 175.
D'AUNOY, R., and VON HAAM, E. (1934): *J. Path. Bact.*, **38**, 39.
DAVISON, K. (1958): *Brit. J. Tuberc. Dis. Chest.*, **52**, 149.
ELLIS, F. H., GRINDLAY, J. H., and EDWARDS, J. E. (1952): *Amer. J. Path.*, **28**, 89.
ELLMAN, P. (1956): *Postgrad. med. J.*, **32**, 370.
EVANS, W., SHORT, D. S., and BEDFORD, D. E. (1957): *Brit. Heart J.*, **19**, 93.
FOWLER, W. M. (1933): *Ann. intern. Med.*, **7**, 1101.
HALL, E. M. (1957): in " Pathology," 3rd Edition, Anderson, W. A. D. London: Kimpton.
MACKENZIE, D. A., and CLAGETT, O. T. (1953): *J. Thorac. Surg.*, **25**, 524.
MUIRHEAD, E. E., and MONTGOMERY, P. O'B. (1951): *Arch. Path. (Lab. Med.)*, **52**, 505.
PIRANI, C. L., EWART, F. E., and WILSON, A. L. (1949): *Amer. J. Dis. Child.*, **77**, 460.
ROSE, G. A., and SPENCER, H. (1957): *Quart. J. Med.*, **26**, 43.
RUSSELL, D. S. (1954): in " Association for Research in Nervous and Mental Diseases," Vol. **34**, p. 160, Baltimore.
STENGEL, A., and WOLFERTH, C. C. (1923): *Arch. intern. Med.*, **31**, 527.
VERLOOP, M. C. (1948): *Acta anat.*, **5**, 171.

Brit. J. Dis. Chest (1959) **53**, 28.

STEROID THERAPY IN PULMONARY FIBROSES

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The advent of steroids placed a valuable additional therapeutic weapon in the hands of the physician treating chest disease and sufficient experience of corticoid therapy in non-tuberculous pulmonary fibroses and infiltrations has since been obtained to allow of some definite conclusions regarding the indications for their use and the degree of improvement that may be expected to result from their employment. This communication examines the place of steroid therapy in pulmonary sarcoidosis, radiation lung damage, the Hamman Rich syndrome and the pulmonary infiltrations occurring in the collagen diseases in the light of personal experience and the published reports of other workers.

I. Sarcoidosis

Before steroids became available a variety of therapeutic measures were used in the treatment of sarcoidosis. Arsenic, gold, urethane, chalmoogra oil, nitrogen mustard, and calciferol as well as ultra-violet light and deep X-ray therapy all had their protagonists and their phases of fashion, but none of them were satisfactory forms of treatment, and their occasional apparent successes were probably attributable to the spontaneous improvement which not uncommonly occurs in the course of the disease. Streptomycin combined with PAS (Hoyle *et al.*, 1955) appeared more effective than any of the earlier remedies, but all are now discarded and largely forgotten and today steroids are the only therapeutic measure employed. Many cases of sarcoidosis are better left without treatment: in fact the only indications for steroid therapy are hypercalcæmia, ocular lesions and pulmonary infiltration. Each of these manifestations responds to corticoid therapy, but it is only with the lung lesions that we are here concerned.

My own experience of the steroid therapy of pulmonary sarcoidosis is limited to 6 cases, 4 of which showed a gratifying response. Brief details of 3 of the 6 cases are given as an indication of the improvement that may be anticipated at the various stages of lung involvement.

Case 1. A male clerical worker aged 23 had had recurrent uveitis for three years. His chest radiograph showed enlarged hilar glands and soft miliary infiltration throughout both lung fields. There was a recent lower motor neurone paralysis of the left seventh cranial nerve. The Mantoux was negative at a dilution of 1 in 100. Previous calciferol therapy had produced no improvement and had severely increased a pre-existing hypercalcæmia. Oral cortisone in a dose of only 50 mg. daily was given for forty-two days. The eyes improved, the serum calcium fell to lower levels, the facial paralysis recovered completely and the miliary shadowing disappeared from the lungs, but the hilar lympha-

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denopathy did not alter. A year later the miliary shadowing had recurred and because of ocular deterioration he was given thirty-two days' steroid therapy, first by ACTH drip and then with oral cortisone. Again the miliary shadowing disappeared from the lungs and on this occasion the hilar lymphadenopathy showed slight reduction. A maintenance dose of cortisone was given for eighteen months and during this time the miliary shadowing did not recur but there was no further shrinkage of the hilar glands. After a further three years with only topical cortisone to the eyes the hilar glands are unchanged, but slight nodular infiltration of harder type is evident in the right mid- and lower zones.

CASE 2. A boy aged 13 gave a history of exertional dyspnœa and enlarged glands in the neck for a year. Examination showed hepato-splenomegaly and lymphadenopathy in the neck, axillæ, inguinal and pre-auricular regions. The chest radiograph showed enlarged hilar glands, but the lung fields were clear. The Mantoux was negative at a dilution of 1 in 100. The blood count, liver function tests and E.S.R. were normal and an X-ray of the hands and feet showed no cystic change. A gland biopsy confirmed the diagnosis of sarcoidosis. A year later he developed conjunctivitis and here again biopsy showed sarcoidosis. After a further six months the parotids became swollen and the chest radiograph showed fibrosis in both lung fields with unchanged hilar gland enlargement. He was treated with 75 mg. of oral cortisone daily for over two years. His conjunctivitis gradually disappeared, his parotid swelling subsided, his spleen and liver became impalpable and the glands in his neck, axillæ and inguinal regions gradually resolved. His exercise tolerance became normal, but there was little radiological change either in his lung fibrosis or his hilar gland enlargement.

CASE 3. A female clerical worker aged 43 gave a history of an attack of iritis twenty-three years previously and of exertional dyspnœa for twenty years. The right eye showed evidence of old iritis and the chest X-ray showed enlarged hilar glands and nodular infiltration in both lung fields, particularly the right. The Mantoux was negative at a dilution of 1 in 100. The E.S.R. was 22 mm. at one hour (Westergren). Over the next eighteen months no change was evident and she was discharged from surveillance. When next seen four years later there was a marked deterioration in exercise tolerance, a gland was palpable above the left clavicle and the chest radiograph showed displacement of the heart and mediastinum to the right and advanced sarcoid with fibrosis in both lung fields, but much more severe in degree on the right side (Fig. 1A).* She has now been treated with 15 mg. of oral prednisone daily for six months. Over the first three months exercise tolerance returned to normal and the chest radiograph improved (Fig. 1B). Since then there has been no further change except a progressive dimunution in the size of the gland above the left clavicle.

It is evident, therefore, that the soft miliary infiltrations (as in Case 1) clear quickly and completely with steroid therapy, but tend to recur and to progress to fibrotic lesions when corticoids are withdrawn. Older lesions in which fibrosis is evident (as in Cases 2 and 3) showed a good subjective response, but only limited radiological improvement can be anticipated. Case 1 also exemplifies the poorer response of the hilar lymphadenopathy as compared with the parenchymal lesions.

* The figures referred to in the text appear on Plates VI-VII.

It is, of course, well known that the soft miliary infiltrations often disappear without treatment. They may persist for as long as five to eight years and then clear completely (Longcope and Freiman, 1952). For this reason it is not considered that such lesions should be treated with steroids unless they are seen to be persistent or progressive or unless they are associated with respiratory disability, which is unusual. Case 1 would not have been treated with steroids for his lung lesion, but the ocular manifestations demanded corticoid therapy. The case illustrates the capacity of steroids to clear the lungs quickly and completely at this stage of the disease. On the other hand, steroid therapy should not be too long withheld, and if there is any diminution in exercise tolerance should be used. If the soft miliary asymptomatic lesions do not clear spontaneously they progress to fibrosis, alveolo-capillary block and secondary emphysema and ultimately right heart failure develops. In these later stages steroid therapy produces only very limited, if any, improvement. Of the two patients among the six observed who showed no response to corticoids, one had advanced fibrosis and gross secondary emphysema. Prolonged administration of cortisone produced no improvement in exercise tolerance and no radiological change. In fact, the only effect appeared to be an increased tendency to superadded respiratory infections, to which he was already prone, and greater difficulty in bringing such episodes under antibiotic control. The other unresponsive case had advanced and long-standing fibrosis and no improvement resulted.

Case 2 illustrates the fact that the lungs may be involved by sarcoidosis long before any parenchymatous change can be detected radiologically. This has been pointed out by Stone *et al.* (1953). In retrospect there is no doubt that this boy should have been given steroid therapy much earlier than he was. Had this been done the response might well have been more satisfactory.

Case 1 illustrates the tendency for pulmonary sarcoidosis to relapse when steroid therapy is withdrawn, and it seems evident that permanent maintenance therapy is required or, alternatively, careful follow-up with a view to resuming treatment should there be any deterioration.

In brief, the indications for steroid therapy in pulmonary sarcoidosis are progressive lesions, lesions showing any tendency to fibrotic change and lesions associated with respiratory disability.

The published reports of the steroid therapy of pulmonary infiltration by sarcoidosis accord closely with our own impressions. All writers are convinced of the therapeutic response. Large series have been treated by Shulman *et al.* (1952), who reported improvement in all of 10 cases, by Lovelock and Stone (1953), two-thirds of whose 12 cases responded; by Israel *et al.* (1954), who reported 26 cases, most of which showed some response; and by Smellie (1958), who noted radiological improvement in 28 of 39 cases. The better results of treatment in recent lesions as compared with older fibrotic changes was pointed out by Siltzbach (1952) and Israel *et al.* (1954), and Smellie (1958) found that all cases treated within two years of discovery of the disease showed radiological response, but only half of those whose lung lesions were of longer standing improved. Subjective improvement without radiological change was noted by

Shulman *et al.* (1952) in 2 of their 10 cases and by Siltzbach (1952) in 2 of his 7 cases. The rapidity of the response to corticoid therapy is exemplified by cases recorded by Sones *et al.* (1951), who found marked radiological improvement in 2 cases treated with oral cortisone for only 11 and 15 days respectively, and by Renold *et al.* (1951) who noted similar radiological improvement and a marked improvement in respiratory function tests after 15 days ACTH drip therapy. The tendency to relapse when steroids are withdrawn has been noticed by many writers (Shulman *et al.*, 1952; Siltzbach, 1952; Riley *et al.*, 1953; Lovelock and Stone, 1953; Israel *et al.*, 1954; Bogart *et al.*, 1954; Hoyle *et al.*, 1955; Smellie, 1958). The literature does not suggest that steroid therapy in pulmonary sarcoidosis carries any increased risk of pulmonary tuberculosis developing.

The effects of pulmonary sarcoidosis on cardio-pulmonary function have been admirably presented by McClement *et al.* (1953), who investigated 10 cases from this point of view. In 4 of the 10 the changes were seen to be chiefly those of pulmonary fibrosis, in 5 predominantly those of alveolo-capillary block, and in the remaining one emphysema was the striking feature. Renold *et al.* (1951), Shulman *et al.* (1952), and Riley *et al.* (1952) all reported an increase in vital capacity, maximum breathing capacity and in PO_2 with steroid therapy.

The poorer radiological response of the hilar glands as compared with the parenchymal lesions was noted by Israel *et al.* (1954). Shulman *et al.* (1952) observed some regression of the hilar glands in 10 of 12 cases treated, but all except 2 relapsed when steroids were withdrawn, and Siltzbach (1952) noted shrinkage in 3 of 7 cases treated and none of these 3 relapsed.

II. Radiation Lung Damage

Among 42 United Birmingham Hospitals patients with radiation damage to the lungs, 9 received steroid therapy. The reasons for the exclusion of the remaining 33 varied. In 6 the lung damage was thought too slight to warrant corticoid therapy and in another 14 the fibrosis was of long standing and considered irreversible. Three were suffering from inoperable bronchial carcinoma and 3 from multiple secondaries, and their prognosis was thought too poor to justify attempts to resolve a secondary disability. Two died very quickly, and the fact that they were suffering from radiation lung damage was not appreciated until too late. In another patient who died while undergoing deep X-ray therapy for widespread lung secondaries the radiation damage was minimal and only recognisable on histological examination. The reasons for withholding steroid therapy in the remaining 4 are of especial interest and importance in the appraisal of its value in radiation lung damage. In one, mild radiation pneumonitis cleared spontaneously, one was improving when the diagnosis was made, and 2 (one fatal and one clearing completely) occurred while on small doses of oral cortisone. The results in the 9 treated cases are shown in Table I.

Our experience suggests (1) that a minimum period of three months'

steroid therapy should be given. (2) That in some cases the damage to the lungs may be so great that a rapidly fatal issue is inevitable. (3) That a good response is only likely in the pneumonitis stage, and when chronic fibrosis has developed no benefit is likely to accrue.

In support of these conclusions brief details of some of the 9 cases treated with steroids and also of some of the untreated cases are recounted.

TABLE I.—RESULTS OF STEROID THERAPY IN NINE UNITED BIRMINGHAM HOSPITALS CASES OF RADIATION LUNG DAMAGE

Result	*Number of cases*	*Remarks*
Greatly improved. Some residual fibrosis	5	3 unilateral cases following post-mastectomy radiotherapy. 2 bilateral cases after radiotherapy for reticuloses.
Death from radiation lung damage	3	2 inadequately treated. 1 died within 48 hours of commencing steroid therapy.
No change	1	Chronic fibrosis of six years' standing.

CASE 7. A male patient aged 18 developed very severe bilateral radiation pneumonitis following cervico-thoracic baths for lymphosarcoma of the cervical glands. He was treated with a daily ACTH drip for twenty-six days and his cough and dyspnœa disappeared, his maximum breathing capacity rose from 71·4l. per minute to 161·04 l. per minute, his vital capacity from 1·3 l to 3.02 l. and his chest expansion from 1¼ in. to 3¼ in., while his chest radiograph showed marked clearing. During the subsequent four weeks cough and dyspnœa returned, the vital capacity fell to 2·32 l. and the maximum breathing capacity to 143·7 l. per minute. After a further course of ACTH symptoms again disappeared, the maximum breathing capacity rose to 185·46 l. per minute and the vital capacity to 2·88 l., while the chest radiograph showed further clearing. He has since remained symptom free except for dyspnœa on severe exertion and his chest X-ray shows only slight residual fibrosis.

CASE 8. A female patient aged 60 developed radiation damage in the upper zone of the right lung ten weeks after post-mastectomy radiotherapy for breast cancer. She was treated with 100 mg. of oral cortisone daily for a month. Her cough and dyspnœa disappeared, her chest radiograph showed marked improvement, her maximum breathing capacity rose from 34 l. per minute to 64 l. per minute and her chest expansion from 1½ in. to 3 in. When next seen eight weeks later there was some return of cough and dyspnœa and the chest radiograph showed some relapse.

These two cases indicate that prolonged steroid therapy is required and that partial relapse occurs after short periods of treatment. Two of the fatal cases were treated at a time when cortisone was in short supply and we had had no experience of its use in radiation lung damage. One was treated for only ten days and the other for only thirteen days. Both died from pulmonary radiation damage, but it is thought both might have survived had more prolonged steroid therapy in higher dosage been employed, especially as one

FIG. 1a.—Case 3. Advanced pulmonary sarcoidosis before steroid therapy.

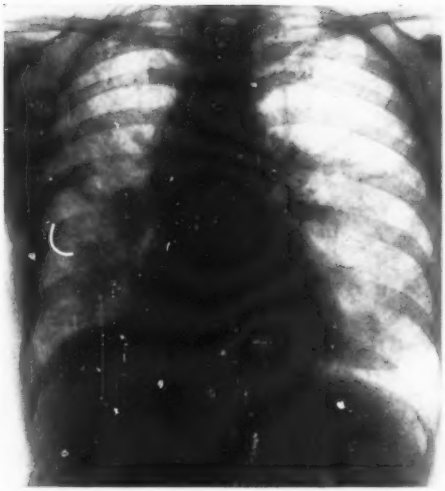

FIG. 1b.—Case 3. Slight radiological improvement after three month's steroid therapy.

FIG. 2a.—Case 63. Systemic lupus erythematosus before steroid therapy. Pericarditis with effusion. Bilateral pleurisy and an area of atelectasis in the right lung.

FIG. 2b.—Case 63. After one year's steroid therapy. The right diaphragm is elevated and there is still atelectasis in the right lower zone.

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FIG. 3.—Case 64. Systemic lupus erythematosus before steroid therapy. A year after commencing corticoids the chest radiograph became normal.

FIG. 4a.—Case 65. Lung fibrosis in scleroderma before steroid therapy.

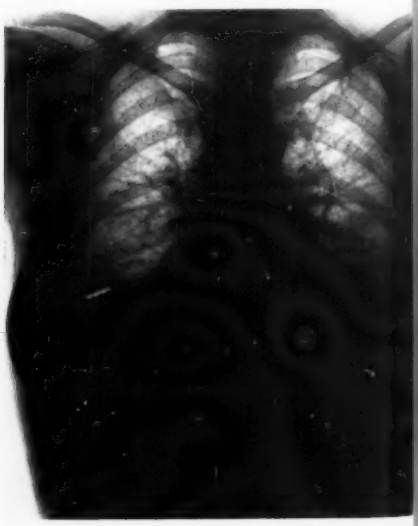

FIG. 4b.—Case 65. Increase in lung fibrosis a eight month's steroid therapy.

of the two showed marked symptomatic and radiological improvement and an increase in his vital capacity and maximum breathing capacity during treatment, but relapse occurred when the cortisone was discontinued.

Four of the 42 patients with radiation lung damage died an asphyxial death in the course of a few days. In 3 of the 4 the cause of the illness was not recognised until death had occurred, and the fourth (previously reported in detail—Whitfield, Lannigan and Bond, 1954) died within 48 hours of commencing steroid therapy. It appears, therefore, that in very severe cases of bilateral radiation pneumonitis the damage to the lungs may be so gross that a fatal issue is inevitable.

Only one patient with chronic fibrosis was given steroid therapy. She was so disabled by cough and dyspnœa that a four months' course of prednisone appeared worthy of trial, but it was not anticipated that much improvement was likely to occur as her fibrosis had been present for six years. Exercise tolerance was not improved, her cough was not relieved, there was no change in her chest radiograph and no improvement in her respiratory function tests (Table II). We were not surprised by the total failure of steroid therapy in this single case and we have not felt an attempt to treat other cases of chronic radiation lung fibrosis with corticoids justifiable.

TABLE II.—RESULTS OF FOUR MONTHS' STEROID THERAPY IN ONE CASE OF CHRONIC PULMONARY RADIATION FIBROSIS

	Cough and dyspnœa	*Vital capacity (litres)*	*Maximum breathing capacity (litres per minute)*	*Chest expansion (inches)*	*Arterial PO_2*	*Chest radiograph*
Before treatment	severe	2·04	46·2	1	80	Bilateral fibrosis chiefly affecting upper zones.
After 8 weeks oral prednisone (15 mg. daily)	no change	2·09	52·4	1½	79	no change
After 16 weeks oral prednisone (15 mg. daily)	no change	1·76	41·8	1½	68	no change

There is no doubt at all that non-fatal radiation damage to the lung improves spontaneously. It usually develops one to three months after the conclusion of radiotherapy to the thorax, and for two or three weeks cough and dyspnœa may be severe and the radiological appearances are those of pneumonitis. Thereafter symptoms gradually regress and the X-ray picture slowly changes to one of fibrosis. In occasional mild cases such as the one mentioned above symptoms may disappear completely and the chest radiograph may return to normal, but usually there is some permanent diminution in exercise tolerance, associated with a dry cough, and the X-ray indicates the presence of some degree of residual fibrosis. This behaviour pattern makes it

difficult to assess the therapeutic value of steroids, but they do appear to produce a very much more rapid improvement than that which occurs spontaneously and the undoubted tendency to relapse with premature withdrawal of the drug is strong evidence in favour of its efficacy. Our present view is that all patients with radiation lung damage that has not reached the stage of chronic fibrosis should be given three months' steroid therapy.

In view of the apparent therapeutic value of steroid therapy in established radiation lung damage we have given oral cortisone (in a dose of 75–100 mg. daily) during, and for three months after, the conclusion of radiotherapy to 6 patients in whom wide field deep X-ray treatment to the thorax with all its attendant dangers was the only hope of curing or palliating their malignant disease. The results in 4 of the cases were wholly satisfactory, but one died from radiation pneumonitis in the course of five days while still taking 50 mg. cortisone daily, and another developed a small area of radiation pneumonitis in one lung which cleared spontaneously while taking a similar dose. It is clear, therefore, that though steroids almost certainly have some therapeutic effect in radiation lung damage their capacity to prevent its development is either limited or non-existent.

Apart from our own publications (Whitfield, Bond and Arnott, 1954 and 1956; Whitfield, Lannigan and Bond, 1954) the literature on steroid therapy of radiation lung damage is limited to four communications. Cosgriff and Kligerman (1951) reported a single case of a woman who developed severe radiation pneumonitis after radiotherapy for a solitary pulmonary metastasis from a colonic carcinoma. Undoubted benefit appeared to result from thirty days' ACTH therapy, but relapse occurred when treatment was stopped; thereafter oral cortisone brought about further improvement. Bluestein and Roemer (1953) described another single case in which bilateral radiation pneumonitis appeared to respond well to oral cortisone. The cough and dyspnœa rapidly disappeared but recurred when the cortisone was stopped, going away again when it was resumed. Three months after starting steroid therapy the chest radiograph was normal. Friedenburg and Rubenfeld (1954) gave 100 mg. of cortisone to 9 patients undergoing radiotherapy to the thorax for one week before treatment, throughout their period of radiotherapy, and for two weeks after its conclusion. None of the 9 developed any evidence of

TABLE III.—THE HAMMAN RICH SYNDROME. RESPONSE TO CORTICOID THERAPY. UNITED BIRMINGHAM HOSPITALS CASES

Sex	*Age*	*Response to steroid therapy*	*Result*
F	28	No response	Fatal issue.
F	63	No response	Alive after 15 months.
F	80	No response	Fatal issue.
M	2½	No response	Fatal issue (Dr. Frances Braid's case. Published in full (Baar and Braid, 1957).)

radiation lung damage, though the period of follow-up was short, only exceeding three months in 4 cases. They also gave details of a case of established radiation lung damage in which cortisone produced marked subjective improvement but little radiological change. On the other hand, Chu *et al.* (1956) reported 8 cases in which prophylactic steroid therapy was given during and after X-ray treatment to the thorax and all of the patients developed radiation lung damage. One of them was given radiotherapy to both lungs at different times

TABLE IV.—THE HAMMAN RICH SYNDROME. PUBLISHED RESULTS OF CORTICOID THERAPY

Result	*Number*	*Sex*	*Age*	*Authors*
No improvement. Fatal issue.	13	F	59	Cox and Kohl, 1952.
		M	2½	Baar and Braid, 1957.
		M	55	Callahan, Sutherland, Fulton and Kline, 1952.
		M	36	Silverman and Talbot, 1953.
		M	38	Schechter, 1953.; Peabody, Buechner and Anderson, 1953.
		F	71	Rubin and Lubliner, 1957.
		F	53	
		M	68	
		M	26	
		F	44	Rubin, Kahn and Pecker, 1952.
		F	9	Bradley, 1956.
		F	42	White and Craighead, 1957.
		F	44	Chernhoff and Hartcroft, 1956.
Temporary subjective improvement. No radiological change. Fatal issue.	4	F	61	Harris, Preuss, Goldman and Freidman, 1957.
		F	72	Peabody, Buechner and Anderson, 1953.
		F	24	Wurm, 1957.
		F	42	Moore, Hamlin and Lindsay, 1957.
Subjective improvement. No radiological change. Alive.	1	F	51	Van Slyck, 1957.
Temporary clinical and radiological improvement. Fatal issue.	1	M	31	Schechter, 1953.; Peabody, Buechner and Anderson, 1953.
Complete remission of symptoms and disappearance of radiological abnormalities. Alive.	1	F	27	Pinney and Harris, 1956.

and developed an equal degree of radiation damage on each side, despite the fact that prophylactic cortisone was given when one side was treated but not during treatment of the other side. They also gave ACTH or cortisone to alleviate established radiation pneumonitis in twelve patients and of these only three showed any radiological evidence of improvement which may well have been spontaneous.

III. THE HAMMAN RICH SYNDROME

The Hamman Rich syndrome is fortunately a rarity. One would have hoped and anticipated that steroid therapy would halt and reverse the interstitial

fibrotic changes in the lungs which produce such a distressing illness with ultimate death from asphyxia and right heart failure, but experience has shown them to be of little value.

Since steroids became available I have only had one case of the Hamman Rich syndrome under my personal care, but through the courtesy of my colleagues in the United Birmingham Hospitals I have been given the opportunity to see 3 others. None of these 4 showed the slightest response to corticoid therapy (Table III) and the results in the much larger group of published cases are almost equally disappointing, only one of 20 responding well (Table IV). No other treatment apart from oxygen, digitalis, diuretics and antibiotics for superadded infections can, however, be offered and steroids must always be given a trial. Peabody *et al.* (1953), however, pointed out the precipitous deterioration that may follow their withdrawal even when no improvement appears to have followed their use.

IV. The Collagen Diseases

(*a*) *Systemic Lupus Erythematosus*

During recent years it has become apparent that systemic lupus erythematosus is not an uncommon disease. The most frequent intrathoracic manifestations are pleurisy and pericarditis, but occasionally the lung itself is involved by an atelectasising pneumonitis.

(1) *Pleural lesions.* Among 10 personally observed steroid treated cases of systemic lupus erythematosus with pleural involvement 7 also had pericarditis and all were acutely ill with high fever and marked dyspnœa. A striking feature was that the severity of the illness and the degree of dyspnœa were much greater than would have been anticipated from the physical signs in the chest or the chest radiograph, which usually showed nothing more than a basal pleural reaction with some elevation and fixity of the diaphragm. Significant pleural effusion occurred in only one of the 10 cases. All showed a dramatic response to corticoid therapy. Pyrexia usually subsided within twenty-four hours and the dyspnœa, pleurisy and pericarditis quickly receded. In one case high dosage had to be given before any improvement occurred, but in all others doses of the order of 200 mg. of cortisone daily or less sufficed to produce rapid and complete resolution of symptoms and signs. In 5 cases withdrawal of steroid therapy or reduction of the dose below 100 mg. of cortisone daily was followed by prompt relapse, but in the other 5 no attempt was made to stop treatment and a permanent maintenance dose of 50-100 mg. of cortisone daily has been continued, and has sufficed to suppress all symptoms.

The published reports of the results of steroid treatment of the pleural manifestations of systemic lupus erythematosus accord closely with our own experience. Ellman and Cudkowicz (1954), Dubois (1956), Ellman (1956) and Hill (1957) all observed a satisfactory response, while Richards (1954) and Harvey *et al.* (1954) found prompt subsidence of fever, rapid relief of dyspnœa and pain, and within a matter of days the disappearance of all clinical and radiological evidence of pleurisy. The 3 cases reported by Richards (1954)

showed a similar tendency to relapse when steroids were withdrawn or the dose reduced to that which we observed.

Many cases of systemic lupus erythematosus have recurrent episodes of pleurisy with fever (Ellman and Cudkowicz, 1954; Harvey *et al.*, 1954; Ellman, 1956), and while it is true that such attacks often subside spontaneously (Dubois, 1956), steroid therapy produces a much more rapid resolution and should always be employed. Thereafter it would appear that permanent maintenance therapy is required in order to prevent relapse and the development of other manifestations of the disease.

(2) *Lung Lesions.* The lung lesions of systemic lupus erythematosus are very much less common than the pleural lesions. I have only observed two such cases treated with steroids and brief details of each of the two is given.

Case 63. A female patient aged 33 had been ill for two months with a rash on her trunk and limbs, dyspnœa, fever and a productive cough. She had pericarditis with effusion, a dry pleurisy on the left side and pleurisy with effusion on the right. In addition the chest radiograph (Fig. 2A) showed an area of atelectasis in the right lung. The serum albumen was 2·5 g. per cent and the serum globulin 4·0 g. per cent. L. E. cells were found in the peripheral blood. Response to steroid therapy was immediate and the pleurisy and pericarditis rapidly resolved. Over a year she has remained well on a maintenance dose of 75 mg. of oral cortisone daily, but the chest radiograph still shows a high right diaphragm and an area of atelectasis in the right lower zone (Fig. 2B).

Case 64. A male patient aged 28 had had anorexia, malaise, and weight loss for four months. He then developed high fever and was found to have splenomegaly, enlarged cervical and axillary lymph glands, albumen, blood and casts in the urine and a blood urea of 67 mg. per cent. The chest radiograph showed opacities in the right lung. The Wassermann was positive in the blood. The white blood cells were reduced to 1,600 per c.mm. and L.E. cells were present in the peripheral blood. Cortisone was given in a dose of 300 mg. daily, but the fever persisted, the hæmoglobin fell to 57 per cent., dyspnœa became severe and the chest radiograph showed increasing pulmonary lesions (Fig. 3). The cortisone was increased to 1 g. daily and a blood transfusion was given. Thereafter he slowly improved and was discharged from hospital three months later on a maintenance dose of 150 mg. of cortisone da . He resumed his work as a builder's labourer after a further twelve weeks and when reviewed five months later his chest X-ray was clear, his hæmoglobin was 114 per cent., his urine was free from albumen and microscopic abnormality, and he had no symptoms of any kind.

The lung lesion of systemic lupus erythematosus is an atelectasising pneumonitis. Baggenstoss (1952) described the details of its pathology and drew attention to the basophilic mucinous œdema of the alveolar walls, peribronchial and perivascular tissues, the alveolar hæmorrhages and the interstitial character of the pneumonitis. Harvey *et al.* (1954) also reported the histological findings in 7 fatal cases and emphasised the chronic interstitial character of the pneumonia and its similarity to the lung lesion seen in polyarteritis nodosa. Hyaline membrane formation, focal necrosis of alveolar walls, capillary thrombi and metaplasia of the bronchiolar epithelium were

features of their cases. Their 7 autopsies were among a total of 138 cases of systemic lupus erythematosus of which 46 had lung lesions. Only 20 of the 46 appeared to have the atelectasising pneumonitis that is part of the disease. In the remaining 26 cases the lung lesions were pyogenic (16), tuberculous (6), aspiration (2) and repeated hæmoptyses (1). Hill (1957) also emphasised the susceptibility to pyogenic lung infections of patients with systemic lupus erythematosus.

Lupus pneumonitis responds less readily and less completely to steroid therapy than do the pleural lesions (Rapaport *et al.*, 1953; Matthews and Meynell, 1954; Ellman and Cudkowicz, 1954; Ellman, 1956; Hill, 1957). Of 9 cases treated with steroids by Harvey *et al.* (1954), the chest radiographs of 2 cleared completely, 4 almost completely and the remaining 3 showed a variable response.

In brief, the interstitial pulmonary lesions of systemic lupus erythematosus should be treated with steroids, and very large doses may be required. Permanent maintenance therapy is indicated, and though excellent results may be obtained the response is less satisfactory than that seen in the pleural and pericardial lesions.

(*b*) *Scleroderma* (*progressive systemic sclerosis*)

Scleroderma is an uncommon disease and only a minority of its victims have lung involvement. In consequence opportunities of treating pulmonary scleroderma are few and I have only seen three such patients treated with steroids, none of whom showed any response as far as the lungs were concerned. Brief details of one of the three cases are given.

Case 65. A woman aged 58 gave a two-year history of Raynaud's phenomenon and tightness of the skin of the hands which showed the characteristic appearances of scleroderma. There was no dyspnœa, but X-rays of the chest showed basal fibrosis (Fig. 4A). Respiratory function tests showed no abnormality. A barium swallow showed œsophageal involvement. The heart, electrocardiogram, liver function tests and blood count were normal. After eight months' treatment with 100 mg. oral cortisone daily the hands are a little better, but the chest X-ray (Fig. 4B) shows the lung fibrosis to have slightly increased.

The literature indicates that the response of pulmonary scleroderma to steroids is usually disappointing. West *et al.* (1951), Hayman and Hunt (1952), Beigelman *et al.* (1953), Ellman and Cudkowicz (1954) and Zion *et al.* (1955) all reported no improvement in the cases they treated; in fact the only recorded cases in which improvement has been noted are one reported by Ellman (1956) and 3 reported by Salomon *et al.* (1955), but in these 3 there was no change in the chest radiographs or the respiratory function tests, the amelioration being limited to a reduction in cough and dyspnoea.

West *et al.* (1951) and Salomon *et al.* (1955) investigated cardio-pulmonary function in their cases and found impairment of alveolo-capillary diffusion. Zion *et al.* (1955) found that such improvement as does occur with steroid

therapy was promptly lost when the drug was withdrawn, so it is clear that in the event of pulmonary scleroderma showing any response to corticoids permanent maintenance therapy will be required if the improvement is to be maintained.

(c) Other Collagen Diseases

I have only observed one patient with pulmonary lesions in polyarteritis nodosa treated with steroids. He showed no response and died nine days after treatment was commenced. The Medical Research Council trial of steroid therapy in polyarteritis nodosa (1957) reports one patient who developed lung lesions whilst under corticoids, but Ellman (1956) reported 3 cases in which the pulmonary lesions responded to steroids. Steroid therapy is all that can be offered to the victims of polyarteritis nodosa and must be employed in every case. Although the lung lesions are of almost as grave prognostic import as is gross renal damage, it is clear that a satisfactory response may occur.

I have not seen any patients with lung lesions in rheumatoid arthritis. Ellman (1956) reported one case which responded well to steroid therapy, but Price and Skelton (1956) observed no improvement in a case under their care and death occurred from right heart failure.

Summary

1. The value of steroid therapy in non-tuberculous pulmonary fibroses and infiltrations is examined in the light of personal experience and the published reports of other workers.

2. Pulmonary sarcoidosis responds well in its earlier stages and steroid therapy should be employed in all patients with respiratory symptoms or with progressive or persistent lung lesions. Permanent maintenance therapy is necessary to avoid relapse.

3. Radiation lung damage in the pneumonitis stage appears to respond to steroid therapy and three months' treatment is suggested for all such cases. Long-standing fibrosis shows no response and corticoids are not thought to have any prophylactic value.

4. The Hamman Rich syndrome is unlikely to respond to steroid therapy, but no other treatment can be offered.

5. The pleural lesions of systemic lupus erythematosus respond dramatically to steroid therapy. The interstitial pneumonitis occurring in this disease shows a less satisfactory response, but both lung and pleural lesions should always be treated with corticoids. Permanent maintenance therapy is required to avoid relapse.

6. The lung lesions of scleroderma are unlikely to be improved by steroid therapy.

I am very greatly indebted to my colleagues in the United Birmingham Hospitals for allowing me to observe patients under their care and to refer to them in this communication. In this respect I am particularly indebted to Prefessor Melville Arnott, Professor K. W. Donald, Mr. W. H. Bond, Mr. C. Rudd, Mr. P. Jameson Evans, Dr. Brian Taylor and Dr. Frances Braid. My thanks are also due to Mr. T. F. Dee for the reproduction of the radiographs.

REFERENCES

BAAR, H. S., and BRAID, F. (1957): *Arch. Dis. Childh.*, **32,** 199.
BAGGENSTOSS, A. H. (1952): *Proc. Mayo Clin.*, **27,** 412.
BEIGELMAN, P. M., GOLDNER, F., and BAYLES, T. B. (1953): *New Engl. J. Med.*, **249,** 45.
BLUESTEIN, S. G., and ROEMER, J. (1953): *J. med. Soc. N.J.*, **50,** 106.
BOGART, A. S., DANIEL, D. D., and FOSTER, K. G. (1954): *Dis. Chest*, **26,** 224.
BRADLEY, C. A. (1956): *J. Pediat.*, **48,** 442.
CALLAHAN, W. P., SUTHERLAND, J. C., FULTON, J. K., and KLINE, J. R. (1952): *Arch. intern. Med.*, **90,** 468.
CHERNHOFF, A. I., and HARTCROFT, W. S. (1956): *Amer. J. Med.*, **21,** 962.
CHU, F. C. H., NICKSON, J. J., and UZEL, A. R. (1956): *Amer. J. Roentgenol.*, **75,** 530.
COSGRIFF, S. W., and KLIGERMAN, M. M. (1951): *Radiology*, **57,** 536.
COX, T. R., and KOHL, J. M. (1952): *Amer. J. clin. Path.*, **22,** 770.
DUBOIS, E. L. (1956): *Ann. intern. Med.*, **45,** 163.
ELLMAN, P., and CUDKOWICZ, L. (1954): *Thorax*, **9,** 46.
ELLMAN, P. (1956): *Postgrad. med. J.*, **32,** 370.
FRIEDENBURG, R. M., and RUBENFELD, S. (1954): *Amer. J. Roentgenol.*, **72,** 271.
HARRIS. M. S., PREUSS, F. S., GOLDMAN, A., and FREIDMAN, N. (1957): *Amer. Rev. Tuberc.*, **76,** 123.
HARVEY, A. M., SHULMAN, L. E., TUMULTY, P. A., CONLEY, C. L., and SCHOENRICH, E. H. (1954): *Medicine*, **33,** 291.
HAYMAN, L. D., and HUNT, R. E. (1952): *Dis. Chest*, **21,** 691.
HILL, L. C. (1957): *Brit. med. J.*, **2,** 726.
HOYLE, C., DAWSON, J., and MATHER, G. (1955): *Lancet*, **1,** 638.
ISRAEL, H. L., SONES, M., and HARRELL, D. (1954): *J. Amer. med. Ass.*, **156,** 461.
LONGCOPE, W. T., and FREIMAN, D. G. (1952): *Medicine*, **31,** 1.
LOVELOCK, F. J., and STONE, D. J. (1953): *Amer. J. Med.*, **15,** 477.
MATTHEWS, H. L., and MEYNELL, M. J. (1954): *Brit. med. J.*, **2,** 1140.
MCCLEMENT, J. H., RENZETTI, A. D., HIMMELSTEIN, A., and COURNAND, A. (1953): *Amer. Rev. Tuberc.*, **67,** 154.
Medical Research Council Report on The Treatment of Polyarteritis Nodosa with Cortisone (1957): *Brit. med. J.*, **1,** 608.
MOORE, F. H., HAMLIN, J. W., and LINDSAY, S. (1957): *Arch. intern. Med.*, **100,** 651.
PEABODY, J. W., BUECHNER, H. A., and ANDERSON, A. E. (1953): *Arch. intern. Med.*, **92,** 806.
PINNEY, C. T., and HARRIS, H. W. (1956): *Amer. J. Med.*, **20,** 308.
PRICE, T. M. I., and SKELTON, M. O. (1956): *Thorax*, **11,** 234.
RAPAPORT, S. I., MEISTER, L., STEELE, F. M., and CANIGLIA, S. R. (1953): *Ann. rheum. Dis.*, **12,** 268.
RENOLD, A. E., FORSHAM, P. H., MAISTERRENA, J., and THORN, G. W. (1951): *New Engl. J. Med.*, **244,** 796.
RICHARDS, D. G. (1954): *Brit. med. J.*, **2,** 777.
RILEY, R. L., RILEY, M. C., and HILL, H. MCD. (1952): *Bull. Johns Hopk. Hosp.*, **91,** 345.
RUBIN, E. H., KAHN, B. S., and PECKER, D. (1952): *Ann. intern. Med.*, **36,** 827.
RUBIN, E. H., and LUBLINER, R. (1957): *Medicine*, **36,** 397.
SALOMON, A., APPEL, B., DOUGHERTY, E. F., HERSCHFUS, J. A., and SEGAL, M. S. (1955): *Arch. intern. Med.*, **95,** 103.
SCHECHTER, M. M. (1953): *Amer. Rev. Tuberc.*, **68,** 603.
SHULMAN, L. E., SHOENRICH, E. H., and HARVEY, A. M. (1952): *Bull. Johns. Hopk.*, **91,** 371.
SILTZBACH, L. E. (1952): *Amer. J. Med.*, **12,** 139.
SILVERMAN, J. J., and TALBOT, T. T. (1953): *Ann. intern. Med.*, **38,** 1326.
SMELLIE, H. (1958): *Brit. med. J.*, **2,** 154.
SONES, M., ISRAEL, H. L. DRATMAN, M. B., and FRANK, J. H. (1951): *New Engl. J. Med.*, **244,** 209.
STONE, D. J., SCHWARTZ, A., FELTMAN, J. A., and LOVELOCK, F. J. (1953): *Amer. J. Med.*, **15,** 468.
VAN SLYCK, E. J. (1957): *Dis. Chest.*, **31,** 593.
WEST, J. R., MCCLEMENT, J. K., CARROLL, D., BLISS, H. A., KUSCHNER, M., RICHARDS, D. W., and COURNAND, A. (1951): *Amer. J. Med.*, **10,** 156.
WHITE, R. B., and CRAIGHEAD, J. T. (1957): *Dis. Chest*, **31,** 335.
WHITFIELD, A. G. W., BOND, W. H., and ARNOTT, W. M. (1954): *J. Fac. Radiol. Lond.*, **6,** 12.
WHITFIELD, A. G. W., LANNIGAN, R., and BOND, W. H. (1954): *Lancet*, **2,** 117.
WHITFIELD, A. G. W., BOND, W. H., and ARNOTT, W. M. (1956): *Quart. J. Med.*, **25,** 67.
WURM, H. (1957): *Beitr. z. Klin. d. Tuberk.*, **116,** 515.
ZION, M. M., GOLDBERG, B., and SUZMAN, M. M. (1955): *Quart. J. Med.*, **24,** 215.

Brit. J. Dis. Chest (1959) **53**, 41.

IDIOPATHIC PULMONARY HÆMOSIDEROSIS IN ADULTS AND ADOLESCENTS

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Until recent years pulmonary hæmosiderosis was considered to occur in two groups of patients (Ellman and Gee, 1951). The first group comprised adults with cardiovascular disease and the second children with severe anæmias—so-called "idiopathic pulmonary hæmosiderosis." It is now recognised that the idiopathic form may also occur in adults, although the number of cases reported in the literature remains comparatively small.

A fairly well defined clinical picture has been evolved of the condition as it occurs in children. In their review of twenty-three cases Wyllie *et al.* (1947) describe periodic attacks of dyspnœa and cyanosis associated with hypochromic anæmia and evidence of hæmolysis. Hæmoptysis, hæmaturia and abdominal pain also occurred in these cases.

A further three cases in adults are reported here and the published cases are reviewed.

Case 1. A man aged 37 was first seen on July 23, 1957. During the previous three months an irritating, unproductive cough had gradually developed. Three weeks before being seen he had a small hæmoptysis which was repeated daily during this time. From the onset of the hæmoptysis he experienced slight dyspnœa on exertion and after a bout of coughing. His only other complaint was of a vague aching pain in the left pectoral region, unrelated to breathing and exertion.

In childhood he had suffered from pneumonia, diphtheria and "shingles," but thereafter had remained perfectly well until 1939 (at the age of 19), when he had an illness which he maintained was similar in all respects to his present one. He spent four and a half months in hospital at this time and the records show that no cause for his hæmoptysis was found, despite numerous investigations. Radiography and fluoroscopy showed no abnormality of the heart or lungs. Bronchoscopy was negative and no tubercle bacilli were found in the sputum. There was no "blood condition" to account for his illness although the patient stated that he was told he was anæmic. He was accepted as fit for the Army and served during the war with only an episode of pneumonia in 1943. In 1950 he had dyspeptic symptons which were attributed to peptic ulceration and which cleared up with diet and alkalis.

His chest had been X-rayed only once between 1939 and 1957. This was in 1948 at a Mass Radiography Unit, the film being reported as normal. This has since been confirmed.

There has been no exposure to industrial hazards apart from a period of two years between 1950 and 1952 when he worked as a coal-miner.

On examination he was well nourished but rather pale. There was no

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increased nail-bed fluctuation and no lymphadenopathy. Medium crepitations were heard at both lung bases and midzones, but the respiratory system was otherwise clinically normal. No abnormality was found on examination of the cardiovascular, alimentary and central nervous systems.

An X-ray of the chest showed fine miliary mottling of both mid- and lower zones. (Fig. 1)*

Following admission to hospital with a clinical diagnosis of idiopathic pulmonary hæmosiderosis, the following investigations were carried out:

Blood: Hæmoglobin 74%.
Red cell count 3·87 M/c.mm.
Colour index 0·95.
White cell count 8,400/c.mm.
Differential count, neutrophil polymorphs 56%.
eosinophil polymorphs 5%.
lymphocytes 35%.
monocytes 4%.
Platelets 310,000/c.mm.
Reticulocytes 5%.
Erythrocyte sedimentation rate (E.S.R.) (Westergren) 17 mm. in 1 hour.
Bleeding time: 3 mins. (Normal 3-5 mins.) Duke.
Clotting time: 4·5 mins. (Normal 4-10 mins.) Lee and White.
Plasma albumin 3·9 G/100 ml.
Plasma globulin 1·0 G/100 ml.
Plasma non-protein nitrogen 34 mg./100 ml.
Serum calcium 9·7 mg./100 ml.

Urine: Albumen, sugar, urobilinogen and microscopy: negative.
Mantoux: 1/10,000: positive.
Intravenous pyelogram: Normal.
Barium meal: Normal.
Sputum: Culture for *M. tuberculosis* negative. Macrophages on a sputum smear were found to contain particles which gave the Prussian blue reaction with potassium ferrocyanide.

Progress: During his stay in hospital he expectorated 30-90 ml. of almost pure blood daily, but remained otherwise symptom-free while at rest in bed. By 14.8.57 his hæmoglobin had fallen to 56 per cent, the anæmia being hypochromic in type, and it was decided to transfuse him with packed cells after bronchoscopy had been performed on 15.8.57.

The report (Dr. A. Pines) was as follows: " Larynx, cords, trachea and main carina normal except for some slight bulging of the left wall of the trachea into the lumen. Both bronchial trees examined and all orifices seen well. The only abnormality was a slow welling of bloodstained froth from all orifices. On sucking away, the froth reappeared in two or three minutes. There were collections of blood in the middle lobe and in the apical lower lobe (left) orifices. A blind biopsy was taken from the left posterior basal bronchus."

Following bronchoscopy the patient complained of pain over the left praecordium and dyspnœa. He became rapidly more dyspnœic and cyanosed and the signs of a left pneumothorax were noted. An intercostal tube was inserted and continuous suction maintained. He was shocked, and during the subsequent nine hours 4 pints of blood were transfused. Auricular fibrillation then developed and he went into right-sided cardiac failure. Despite treatment with intravenous digoxin and diuretics his condition deteriorated and he died some twenty hours after bronchoscopy.

* The figures referred to in the text appear on Plate VIII.

Post-mortem examination was performed by Dr. J. M. Drennan.

Relevant findings:

Lungs: Both lungs are voluminous, consolidated and heavy. The cut surface of the lungs shows uniformly consolidated lung parenchyma, dark brown in colour with patches of black and of rusty brown. Only a small amount of lung parenchyma at the apices of the lungs show the normal aerated appearance.

The trachea and bronchi contain a considerable amount of altered blood.

The hilar and mediastinal lymph nodes are all slightly enlarged and loaded with carbon pigment, but show no other obvious change. The pulmonary vessels appear normal.

Heart: The coronary arteries are patchily atheromatous but of adequate calibre throughout. The right ventricle is markedly dilated but not hypertrophied. The other chambers of the heart are normal as also are the valves and myocardium. The aorta is patchily atheromatous throughout its length.

Spleen: (150 g.) Slightly enlarged.

Endocrines: The adrenals are slightly smaller than normal, the cortical zones diminished in depth and pale yellow in colour.

Histology:

Lungs: Sections taken from all parts of both lungs show much the same pathological picture. The alveoli are full of recently shed blood or protein-rich œdema fluid and all alveoli contain numerous hæmosiderin-laden macrophages. The latter sometimes form a compact mass of cells occupying the whole alveolar space. The few air-containing alveoli are distended and thin-walled—compensatory emphysema. Occasional areas of deflated lung are encountered in most of the sections. The alveolar walls, in the areas of hæmorrhage, are thickened by a lining of proliferated macrophagic alveolar cells, with or without hæmosiderin granules. There does not appear to be any connective tissue increase in the lung parenchyma and the elastic fibres everywhere are free from iron incrustation. Polymorph and lymphocyte infiltration is not seen anywhere in the sections.

A considerable number of dilated alveolar ducts are lined by a deeply stained " hyaline membrane "; some contain clotted blood. The bronchioles are full of blood. The walls of pulmonary vessels of all calibres are normal. Nowhere is there any appearance of allergic vasculitis.

Hilar lymph nodes: The lymphoid sinuses contain a considerable number of macrophage cells, most of which contain hæmosiderin granules.

Spleen: Occasional hæmosiderin-containing cells are present in the pulp of the spleen.

Bone marrow: There is a moderate increase in hæmopoietic activity, principally along the line of erythrocyte differentiation, with a notable increase in nucleated red cells.

Comment: The post-mortem findings in this case justify the diagnosis of idiopathic hæmosiderosis. Examination of the lung at post-mortem showed that the final bleeding episode involved a wide area of lung parenchyma and was severe and that previous hæmorrhages were slight and/or infrequent without producing any appreciable pulmonary fibrosis. Lung changes of this sort have been observed in several of the reported cases of idiopathic pulmonary hæmosiderosis in adults.

CASE 2. In March 1953 a 33-year-old naval rating was found, on routine X-ray examination of his chest, to have miliary stippling throughout both lung fields, less marked at apices and bases (Fig. 2). His only complaint was slight dyspnœa on exertion for the previous two months.

Clinical examination was entirely normal. Sputum was negative for tubercle bacilli, his E.S.R. was 5 mm. in one hour and Mantoux 1 : 10,000 was positive. A lymph gland biopsy from the left supra-clavicular triangle showed chronic inflammatory changes only.

He was then investigated in hospital. Wassermann reaction (W.R.) and liver biopsy were normal, but lung biopsy established a diagnosis of idiopathic pulmonary hæmosiderosis.

He was invalided from the Royal Navy in September 1953 and has since been followed up at the Royal Victoria Dispensary, Edinburgh. By October 1953 there was marked clearing of the X-ray, and when last seen in April 1957 the film was virtually normal apart from calcified spots at the left apex and both hila (Fig. 3). During this time also he remained symptom-free and at work. The slides of the original biopsy have been reviewed and the diagnosis has been confirmed.

CASE 3. A 19-year-old female domestic servant was admitted to hospital on November 2, 1957. During the previous five years she had had several episodes of hæmoptysis, pyrexia and anæmia. On three occasions she had been admitted to other hospitals. While in one of these, during January 1953, the following investigations were done:

Haemoglobin 82%.
Red blood count 4·2 million/c.mm.
White blood count 9,500/c.mm.
E.S.R. 14 mm. in 1 hour.
Mantoux 1 : 10,000 positive.
W.R. and Kahn negative.

Chest X-ray report: " Loss of translucency in both lower zones, but this is probably due entirely to soft tissue shadows. Slight mottling is visible in the left mid-zone suggesting old infection."

On admission to another hospital in August 1953 for investigation of anæmia, findings were as follows:

Haemoglobin 5·41 g.%.
Packed cell volume (P.C.V.) 21·0%.
Mean Corpuscular Hæmoglobin Content (M.C.H.C.) 25·8%.
Serum iron 25 μg. %.
Sternal marrow—normoblastic hyperplasia only.
X-ray of chest—normal.

She was considered to have a pure iron deficiency anæmia and was treated with full doses of iron.

For two months before her present admission she had felt breathless on exertion and had a cough productive of bright red blood. In addition she felt giddy, had headaches and had fainted.

On examination she was pale and had a pyrexia of 101·4% F. Apart from tachycardia of 120/min. and a mitral systolic murmur, physical examination was negative.

Investigations:

Hæmoglobin 48% (7·1 g. %).
Red blood count 3·19 million/c.mm.
P.C.V. 25%.
M.C.V. 78 c.μ.
M.C.H.C. 28%.
Reticulocytes 7%.
White blood count 12,000/c.mm.
Neutrophils 63·5%.
Lymphocytes 31·5%.
Monocytes 4·0%.
Eosinophils 1·0%.
E.S.R. 25 mm./hr. (Westergren).
Serum bilirubin 0·8 mg.%.
Serum proteins: Total 7·0 g.% (Albumin 4·6 g.%, Globulin 2·4 g.%).
Electrophoresis—normal pattern.
Alkaline phosphatase 8 King Armstrong units.
Thymol turbidity 1·5 units.
Urine—no abnormality.
X-ray of chest: "Fine stippled opacities throughout both lung fields, but mainly in the mid- and lower zones." (Fig. 4.)
Sputum: No pathogenic organisms isolated on culture. Many large mononuclear cells of the histiocyte type were seen to contain coarse yellow-brown granules which gave a positive Prussian blue reaction.

Progress: For several days she had slight pyrexia and throughout her six weeks' stay in hospital had continuous slight hæmoptysis. Her general condition improved after her hæmoglobin had been raised to 90% by blood transfusion. Oral iron was given and prednisolone 20 mg. daily for fourteen days was tried, but without effect on the hæmoptysis or rate of clearing of the X-ray picture. At the time of her discharge from hospital her X-ray had cleared, though incompletely, and she still had slight hæmoptysis. When seen six weeks later she remained slightly dyspnœic on exertion and still expectorated 10-15 ml. of blood daily. The X-ray had shown further slight improvement.

Comment on Cases

Case 1 was 37 years old when the diagnosis was made. There is little doubt, however, that his illness at the age of 19, consisting as it did of dyspnœa, hæmoptysis and anæmia, and in spite of the negative chest X-ray, was an episode of idiopathic pulmonary hæmosiderosis. A remission in this disease, lasting as long as eighteen years, is indeed remarkable. The diagnosis was made on clinical grounds and confirmed at autopsy.

The fact that there may be few symptoms is illustrated by Case 2, where the diagnosis was eventually established by lung biopsy. The remission in this case has again been complete and has lasted five years. Radiological clearing has also been complete.

In Case 3 the history of repeated episodes of anæmia and hæmoptysis is that typically obtained in children with this condition. The correct diagnosis was not considered until the chest X-ray was unequivocally abnormal and hæmosiderin-laden macrophages were sought and found in the sputum.

Discussion

In the older literature this condition is sometimes referred to as "essential brown induration of the lungs" and was also, unfortunately, occasionally

TABLE I.—AGE AND SEX OF REPORTED CASES

Case	*Authors*	*Sex*	*Age at onset of symptoms*	*Age at death*	*Age at last follow-up*
1	Borsos-Nachtenebel (1942)	M	?	38	—
2	Waldenström (1944)	F	16	19	—
3	Walton and Williams (1951)	M	16	19	—
4		M	20-30	?	?
5		M	20-30	?	?
6	Kerley (1951)	F	20	?	?
7		M	19	?	?
8		M	28	—	32
9	Tait and Corridan (1952)	M	31	31	—
10	Cliff (1953)	M	20	—	22
11	Herzog (1954)	M	6	26	—
12	Hamer (1955)	M	13	—	19
13	Cliff (1955)	M	27	—	28
14	Glück (1955)	M	15	17	—
15	Meyer (1955)	M	20	—	22
16	Wagner (1955)	F	21	25	—
17	Chatgidakis (1955)	F	47	47	—
18	Bruwer *et al.* (1956)	M	16	21	—
19		M	24	25	—
20	Browning and Houghton (1956) ..	M	18	22	—
21		M	24	—	30
22	Florian (1956)	F	27	27	—
23	Halmágyi *et al.* (1956)	M	38	—	40
24	Wynn-Williams and Young (1956) ..	M	28	—	26
25	Matzel (1957)	F	29	32	—
26	Doering and Gothe (1957)	M	7	17	—
27		M	19	37	—
28	Author's cases	M	33	—	36
29		F	14	—	19

bracketed with hæmochromatosis, to which, of course, it has no relation as there is no general upset of iron metabolism. Since Ceelen (1931) was the first to describe a case (in a child) it is also labelled " Ceelen's disease."

The first report of idiopathic pulmonary hæmosiderosis occurring in a person of over 16 years of age was made by Borsos-Nachtnebel (1942). Subsequently cases have been recorded by Waldenstrom (1944), Walton and Williams (1951), Tait and Corridan (1952), Cliff (1953), Herzog (1954), Hamer (1955), Cliff (1955), Glück (1955), Meyer (1955), Wagner (1955), Chatgidakis (1955), Bruwer *et al.* (1956), Browning and Houghton (1956), Florian (1956), Halmágyi *et al.* (1956), Wynn-Williams and Young (1956), Matzel (1957) and Doering and Gothe (1957). Kerley in discussing this condition in a " Textbook of X-ray Diagnosis " (2nd ed., 1951) mentions five cases.

Sex and Age Incidence

Many more males than females are affected (in the ratio of 3 : 1), whereas in the childhood cases females predominate in the ratio of 2·5 : 1 (Wyllie *et al.*, 1948). The sex incidence in the adult cases corresponds with the greater

frequency of secondary pulmonary hæmosiderosis from mitral stenosis in men as opposed to women, although mitral stenosis is commoner in women (Florian, 1956). There is no evidence of a familial incidence.

In only four of the adult cases did symptoms begin after the age of 30, the oldest being 47. Details of age and sex in twenty-nine reported cases are given in Table I.

Clinical Features

This is a disease characterised by remissions and relapses, although the patient may die in the first episode. In the cases which ended fatally the time interval between onset of symptoms and death varied from three months to twenty years (mean 5·4 years). Where complete remissions occurred these varied from a few months to eighteen years, the majority lasting several months. In those remaining alive the survival period has varied from one to six years (mean 3·4 years) and remissions have lasted from a few months to four years.

Where clinical data have been given, dyspnœa, although sometimes slight, has been a constant feature. Cough and hæmoptysis have been almost invariable. In a few cases, however, the sputum has been merely blood-streaked, while in two hæmoptysis was massive and terminal. The demonstration of hæmosiderin-containing macrophages in the sputum was an important factor in the diagnosis in many cases. In children, examination of gastric contents for these cells is of value. This test constitutes a strong confirmatory finding in patients without heart disease (Browning and Houghton, 1956).

Anæmia has occurred in the majority of cases. This has been of the iron-deficiency type with features indicating increased red blood cell destruction (raised serum bilirubin and excess urinary urobilinogen). The bone marrow, when examined, has been normoblastic and hyperplastic, reflected by the reticulocytosis in the peripheral blood. In some cases with marked pulmonary changes there has been polycythæmia, probably because of arterial oxygen unsaturation. The serum iron is low and often remains low when the hæmoglobin has returned to normal (Florian, 1956).

Cyanosis was not encountered in as many cases as might be expected, probably because of the associated severe anæmia.

Many cases had pyrexia at some time during the course of the illness, and of the less common clinical features headache occurred in five. Only three cases were reported as having enlargement of liver or spleen and two complained of abdominal pain. In three instances finger clubbing was present and in one of these cases the toes were also markedly clubbed. A single instance of unexplained hæmaturia is also mentioned.

Radiological Findings

The typical X-ray abnormality is a diffuse mottling of both lung fields, the shadows usually being pin-point to 3 mm. in diameter and generally affecting the mid- and lower zones. The hilar shadows are sometimes enlarged.

There may occasionally be evidence of segmental collapse and more confluent shadowing associated with hæmoptysis.

In only one of the reported adult cases, that of Tait and Corridan (1952), was radiological abnormality lacking. X-rays taken throughout the illness and up to two and a half months from death were normal, although the typical pathological changes were present in the lungs at autopsy. In fourteen cases a radiological abnormality developed at varying periods after the onset of symptoms, and it is probably worth stressing that an acute episode of the disease may occur with a normal chest X-ray. In many instances some resolution occurred during the course of the illness, and in five cases there was complete radiological clearing during a natural remission. Details are given in Table II.

TABLE II.—RADIOLOGICAL FINDINGS

Case	*Typical abnormality from beginning*	*Abnormality developing after onset of symptoms*	*Resolution during course of illness*	*Complete resolution during remission*	*No radiological abnormality*
2	+	—	+	—	—
3	—	About 1 year	—	—	—
9	—	—	—	—	+ (2½ months before death)
10	+	—	—	+	—
11	—	About 11 years	—	—	—
12	—	About 5½ years	—	—	—
13	—	About 1 year	—	+	—
14	—	About 1 year	+	—	—
15	+	—	—	—	—
16	—	About 2 years	+	—	—
17	+	—	—	—	—
18	+	—	—	—	—
19	—	About 1 year	—	—	—
20	—	About 4 years	+	—	—
21	—	About 1 year	—	+	—
23	+	—	—	—	—
24	—	+	—	—	—
25	—	About 18 months	—	+	—
26	—	About 6 months	—	—	—
27	—	18 years	—	—	—
28	+	—	—	+	—
29	—	About 1 year	+	—	—

Treatment

As the ætiology of idiopathic pulmonary hæmosiderosis remains unknown, effective therapy is lacking. In all the cases with anæmia iron was given with satisfactory response. In eleven cases blood transfusion was necessary at some stage of the illness.

In three cases an erroneous initial diagnosis was made. Streptomycin had no effect in one diagnosed as miliary tuberculosis, and radiotherapy and

FIG. 1.—Case 1. Detail from right mid-zone in chest radiograph showing fine miliary shadowing.

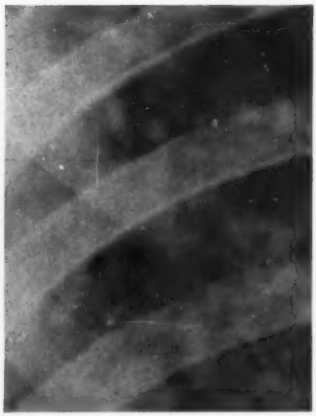

FIG. 2.—Case 2. Detail from right mid-zone in chest radiograph showing diffuse mottled opacities.

FIG. 3.—Case 2. Detail from right mid-zone in chest radiograph showing clearing of opacities after five years.

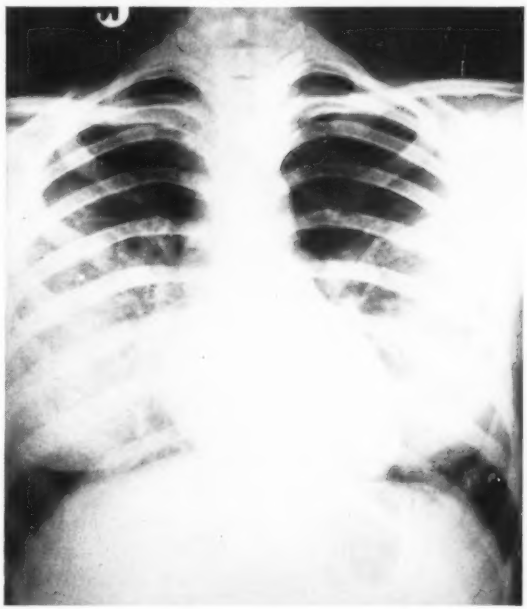

FIG. 4.—Case 3. Chest radiograph showing distribution of opacities in mid and lower zones of both lung fields.

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"Trimethanin" were given without effect to another case diagnosed as Hodgkin's disease. A third case, diagnosed as having an acute reticulosis, was said to benefit from radiotherapy.

Corticosteroids have been given in three of these cases. In one case cortisone was administered in unstated dosage six weeks before death without apparent effect. Browning and Houghton gave 15 mg. ACTH by drip over eight hours daily to one of their cases and followed this after two weeks with 100 mg. cortisone daily for some three months. The patient had remained in satisfactory remission at the time of writing. One of the cases recorded here was given 20 mg. prednisolone daily without radiological or clinical amelioration.

It is of interest to note here the case recorded by Wagner (1955)—a 25-year-old woman became pregnant during the course of her illness but remained well during the pregnancy. Shortly after childbirth she had a relapse and despite treatment died in the sixth week of the puerperium.

In one case splenectomy had been performed with no effect on the disease.

An interesting suggestion as to treatment is made by Doering and Gothe (1957). On the theory that there is increased laying down of iron in the lung (see below) they discuss the use of chelating agents, particularly ethylenediaminetetra-acetic acid (EDTA), in an attempt to remove iron from the lung. They point out, however, that the increased urinary output is very small and that other iron stores in the body would be depleted. Wishinsky *et al.* (1953), using EDTA for the mobilisation and removal of iron in a case of hæmochromatosis, found a threefold increase of urinary iron during administration of the drug.

It must be remembered, however, that claims for any therapeutic measure in this condition which is characterised by long and complete natural remissions must be viewed critically.

Prognosis

This is generally regarded as serious. Of the twenty-nine cases reported in persons over 16 years of age, ten survived at the time of writing, the fate of four was not mentioned and the rest had died. Schaar and Rigler (1956), reviewing forty cases occurring in persons under 16 years of age, stated that only fifteen were surviving at the time of the report. In the adult cases remissions may be of several years' duration.

Pathogenesis

This condition is associated with repeated intra-pulmonary bleeding, resulting in the deposition of hæmosiderin in the lungs. Microscopically the alveoli and alveolar walls are infiltrated with hæmosiderin-laden macrophages and free hæmosiderin. Capillaries are thickened, fibrous tissue in the inter-alveolar septa is increased, while elastic tissue is decreased.

Many authors, including Ceelen (1931) and Waldenström (1944), have suggested that there is a primary defect in the pulmonary vessels, particularly involving the elastic fibres. Wylie *et al.* (1948) postulate that decrease of elastic fibres in the pulmonary interstitial tissue leads to lack of distensibility of the

lungs with consequent peripheral vascular stasis. This is followed by "hæmorrhage by diapedesis" and deposition of hæmosiderin. Nancekievill (1949), however, found no evidence of deficiency in the elastic fibres of vessels or alveoli, and he considers that the changes in the elastic fibres are the result rather than the cause of the hæmosiderosis.

McLetchie and Colpitts (1949) attempt to explain the periodicity of attacks by postulating that the primary abnormality is one of defective vasomotor control of capillary tone.

Steiner (1954) considers that the disease is caused by an auto-antibody antigen reaction with the lung as the shock organ. For this reason he has advocated splenectomy as treatment in children, and claims reduction in the number of attacks following this operation.

Probst (1955) showed that there is an increase in acid mucopolysaccharide (AMPS) within the elastic fibres of the small blood vessels. The elastic fibres are thereby weakened, the blood vessels dilate and bleeding by diapedesis occurs. Iron is liberated and as AMPS has a strong affinity for it, iron becomes encrusted on the elastic fibres. This further weakens blood vessels and the process extends to larger vessels. The actual cause of the increase in AMPS is unknown, but the author draws an analogy with the condition of senile elastosis and also suggests that it might be a form of arachnodactyly.

Further information concerning iron in the lung was obtained by Doering and Gothe (1957) with radioactive iron studies. Using Fe^{59} they showed a raised turnover of serum iron and increased laying down of iron in the lungs.

Summary

Three cases of idiopathic pulmonary hæmosiderosis occurring in adults are described.

Twenty-nine published cases of this condition in persons over 16 years of age are reviewed.

The commoner clinical features are dyspnœa, hæmoptysis and anæmia. Less commonly there is pyrexia, headache, hepatosplenomegaly, abdominal pain and finger clubbing. Natural remissions are frequent and may last as long as eighteen years.

The typical radiological abnormality of miliary mottling, usually in mid- and lower zones, is almost always present at some stage of the disease. An acute episode may occur without chest X-ray changes.

There is no effective treatment.

The prognosis is serious. Ten of the twenty-nine published cases were alive at the time of writing.

The most recent work on the pathogenesis of the disease suggests that the elastic fibres of the small blood vessels of the lung are weakened by an increase in acid muco-polysaccharide. An analogy with senile elastosis and arachnodactyly is made.

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REFERENCES

BORSOS-NACHTNEBEL, E. (1942): *Zbl. allg. Path. path. Anat.*, **79,** 174.

BROWNING, J. R., and HOUGHTON, J. D. (1956): *Amer. J. Med.*, **20,** 374.

BRUWER, A. J., KENNEDY, R. L. J., and EDWARDS, J. E. (1956): *Amer. J. Roentgenol.*, **76,** (1), 98.

CEELEN, W. (1933): In "Handbuch des speziellen pathologischen Anatomie und Histologie," Vol. 3, Part III, p. 20. Berlin: F. Henke and O. Lubarsh.

CHATGIDAKIS, C. P. (1955): *S. Afr. J. Lab. clin. Med.*, **1,** 166.

CLIFF, J. M. (1953): *Brit. J. Radiol.*, **26,** 102.

CLIFF, J. M. (1955): *Brit. med. J.*, **1,** 1340.

DOERING, P., and HANS-DIETER GOTHE (1957): *Klin. Wschr.*, **35,** 1105.

ELLMAN, P., and GEE, A. (1951): *Brit. med. J.*, **2,** 384.

FLORIAN, J. (1956): *Münch. med. Wschr.*, **98,** 1597.

GLÜCK, E. (1955): *Acta path. microbiol. scand.*, **37,** 214.

HALMÁGYI, D., FELKAI, B., SÖVERNYI, E., WEBER, A., CYIPOTT, Z., KOVACS, G., and STEINER, B. (1956): *KreislForsch.*, **45,** 40.

HAMER, N. A. J. (1955): *Brit. med. J.*, **1,** 1008.

HERZOG, G. (1954): *Ber. oberhess. Ges. Nat.-u Heilk.*, **27,** 199.

KERLEY, P. (1951): "A Textbook of X-ray Diagnosis," 2nd ed., Vol. 2, 181. London: H. K. Lewis.

MCLETCHIE, N. G. B., and COLPITTS, G. (1949): *Canad. med. Ass. J.*, **61,** 129.

MATZEL, VON W. (1957): *Dtsch. med. Wschr.*, **82,** 2194.

MEYER, K. (1955): *Ärztl. Wschr.*, **25,** 583.

NANCEKIEVILL, L. (1949): *Brit. med. J.*, **1,** 431.

PROBST, A. (1955): *Virchows Arch.*, **326,** 633.

SCHAAR, F. E., and RIGLER, L. G. (1956): *JL-Lancet*, **76/5,** 125.

STEINER, B. (1954): *Arch. Dis. Childh.*, **29,** 391.

TAIT, G. B., and CORRIDAN, M. (1952): *Thorax*, **7,** 302.

WAGNER, K. (1955): *Medizinische*, 117.

WALDENSTRÖM, J. (1944): *Acta radiol.*, **25,** 149.

WALTON, M., and WILLIAMS, A. A. (1951): *Brit. med. J.*, **2,** 390.

WISHINSKY, M., WEINBERG, T., PREVOST, E. M., BURGIN, B., and MILLER, M. J. (1953): *J. Lab. clin. Med.*, **42,** 550.

WYLLIE, W. G., SHELDON, W. BODIAN, M., and BARLOW, A. (1948): *Quart. J. Med.*, **17,** 25.

WYNN-WILLIAMS, N., and YOUNG, R. D. (1956): *Thorax*, **11,** 101.

Brit. J. Dis. Chest (1959) **53**, 52.

THE PROGNOSIS IN SYPHILITIC AORTIC ANEURYSM AFTER TREATMENT WITH PENICILLIN

By Richard Ward and Lucien Read

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The prognosis of patients suffering from syphilitic aortic aneurysm, although varying widely and being influenced by occupation and age of onset, is undoubtedly very poor. Kampmeier (1938) stated that, with comparatively few exceptions, the duration of life after the onset of symptoms in aneurysm of the aorta was to be measured in months. Grimble (1955), in a review of patients with cardio-vascular syphilis treated in the days prior to penicillin, showed that arsenic roughly doubled the expectation of life; in a selected group of patients untreated the duration of life averaged 15·6 months from the onset of symptoms. It was natural, therefore, that attempts by surgical means should be made to eliminate one of the major causes of death in these cases, namely rupture of a saccular aneurysm. For example, Borrie and Griffen (1950) used Colt's umbrella in nine cases; of these four died within the following sixteen months. Successful resection of saccular aneurysms has been accomplished on a number of occasions. Bahnson (1954) operated upon eleven patients. The operations were technically difficult and in five only was a satisfactory result obtained.

There have been few accounts of the effect of penicillin on the prognosis in this disease; Moore (1949) in treating six cases of saccular aneurysm did not have encouraging results, since, of these, two ruptured within six months of completing treatment. O'Brien *et al.* (1955) treated five cases of saccular aneurysm with penicillin and four of these were alive at the end of a five-year follow-up. They concluded that penicillin may have been more effective than metal therapy in halting the syphilitic process and prolonging life.

It is the object of this paper to discuss thirteen cases of syphilitic aortic aneurysm treated with penicillin.

Material

This small group comprised seven females and six males, who had been observed for periods between 20 and 74 months. Their ages varied between 55 and 73 years. There were nine saccular and four fusiform aneurysms, and all patients had positive serological reactions for syphilis. It is not intended to discuss in detail the symptomatology except to emphasise that all patients when referred to us were definitely symptomatic. Pain, dysphagia and hoarseness were the most common complaints. The diagnosis was always easy to make with the aid of X-ray screen examination and films. It is interesting to note that two patients presented with superior vena caval obstruction and

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remain well at the time of writing this report. Coincident aortic regurgitation was present in four cases, and three showed evidence of neurosyphilis.

Treatment

No case had received any therapy prior to coming under our care. The earlier patients were given potassium iodide in a dosage of 60 gr. daily for three weeks before starting treatment with penicillin. Soon this was given up, as there appeared to be little evidence that it had any effect on syphilitic lesions with the exception of cutaneous gummata. Each patient, therefore, received a daily injection of 600,000 units of procaine penicillin until a total of 20 mega units had been given. This constituted the complete treatment and the course was not repeated.

Herxheimer Reactions

Two patients had Herxheimer reactions, cases 2 and 4. In each there was a sudden " collapse " with fall of blood pressure and associated weakness. Both patients recovered in a few hours. Subsequent electrocardiography did not show any evidence of myocardial infarction and treatment with penicillin was continued the next day. It appears that this reaction is of the " all or none " type (*Bull. World Health Organisation*, 1954, quoted by *Lancet* leading article, 1954, and Moore *et al.*, 1949), and that there is, therefore, no valid reason for starting treatment in these cases with a dose of penicillin which is therapeutically inadequate. The available clinical and experimental evidence (Sheldon *et al.*, 1952) still points to the Herxheimer reaction as being a hypersensitivity response.

Results

Of the thirteen cases treated, three have died during the follow-up period, none as a result of rupture of the aneurysm (see table). Two of these patients were amongst the oldest in the group and the third had aortic regurgitation. Of the others, nine are leading relatively normal lives, and one is subject to attacks of left ventricular failure. After treatment, there was complete relief of pain (five cases in which it was present), in all cases a feeling of well-being, improvement in phonation, disappearance of dysphagia and cessation of hæmoptyses. In six cases there was a great gain in weight necessitating considerable restriction of food intake later. There was no change in the signs of superior vena caval obstruction (two cases). In some we have noted the occurrence of pulsation in the wall of the aneurysm when it had not been present before treatment. In Case 1 there was rapid and considerable increase in size of the aneurysm, but although he died 20 months after completion of treatment, death was, according to his general practitioner, due to bronchitis and heart failure and not to rupture. The saccular aneurysm present in Case 2 also increased in size (see Case Report), but the patient has remained free from his original complaint of left upper chest pain and leads an active life. There was no alteration in the serological tests following therapy in any case.

TABLE OF CASES

Case No.	*Age on diagnosis*	*Sex*	*Saccular or fusiform*	*Observation after therapy (months)*	*Comment*
1	70	M	S	20	Died, according to general practitioner from bronchitis and heart failure.
2	60	M	S	52	Normal life but not at work.
3	65	F	F	32	Attacks of bronchitis.
4	65	F	S	35	Getting about well despite great gain in weight. Dieting.
5	74	F	F	26	Died.
6	64	M	S	64	Was working as bookmaker's runner four years after diagnosis and treatment. Aortic regurgitation present.
7	58	M	F	32	Walking two miles; swallowing improved.
8	58	F	S	35	Carcinoma of colon removed one year after completion of treatment. Reasonably well and enjoying an active life.
9	63	M	F	65	Incipient left ventricular failure. Aortic regurgitation.
10	61	F	S	74	Ovarian cyst removed without incident three years after treatment. Aortic regurgitation.
11	73	M	S	68	Able to walk 2 miles.
12	57	F	S	60	Does all house work and cares for invalid husband.
13	55	F	S	48	Died four years after diagnosis and treatment from bronchopneumonia. Aortic regurgitation.

Illustrative Case Histories

CASE 2. A 60-year-old man employed by the corporation, loading dustbins and driving a horse wagon, was referred in November 1953, complaining of a dull aching pain in the left shoulder and upper part of the left chest at the back and front, present for five months. In addition, he had had an occasional feeling of faintness during the preceding five years. Clinical examination showed a thin, healthy-looking man, with systolic pulsation in the second left interspace and beneath the third left rib close to the sternum. Aortic second sound loud and "ringing." B.P. 130/70, no aortic regurgitation. There was no clinical evidence of neurosyphilis. W.R. and Kahn were strongly positive. Screening did not show any pulsation of the wall of the aneurysm. (Figs. 1 and 2.)*

Treatment and Progress. He was admitted to hospital, treated with penicillin and had a mild Herxheimer reaction. By January 1954 he was free from pain and screening showed slight pulsation in the wall of the aneurysm. One year later he had gained a stone in weight and was symptom free. In 1956 the sternal pulsation was more marked, but apart from some attacks of faintness he was well. Increased size of the aneurysm is shown four years after treatment. (Fig. 3.)

* The figures referred to in the text appear on Plate IX.

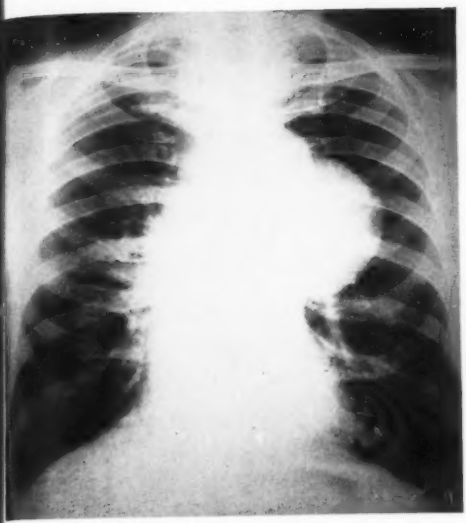

Fig. 1.—Case 2. Postero anterior view. November, 1953.

Fig. 2.—Lateral view.

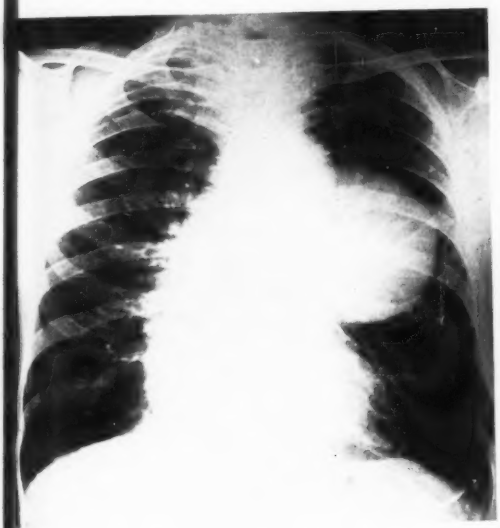

Fig. 3.—Case 2. December, 1957.

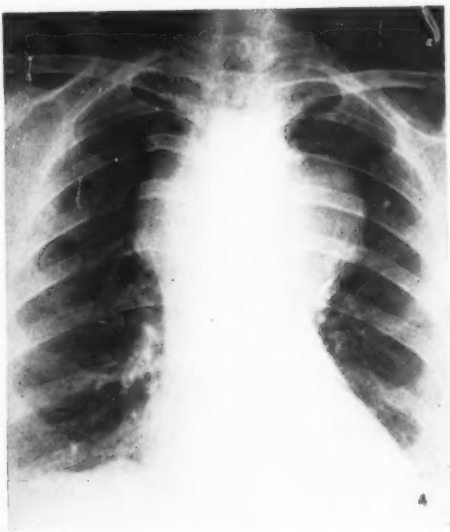

Fig. 4.—Case 4.

CASE 4. In March 1955 this 67-year-old woman was referred by a colleague in the E.N.T. department to one of us. For two months she had felt exhausted, breathless, had difficulty in swallowing and had a brassy cough. On examination she looked ill, had pale mucosæ, non-pulsatile distension of the external jugular veins and fullness of the lower part of the neck. B.P. 200/110; pulsation in the second and third right interspaces. Left pupil smaller than right, both irregular and with sluggish reaction to light. W.R. and Kahn strongly positive. Investigations in hospital showed the *C.S.F. W.R.* to be positive with luetic type of Lange curve. Both vocal cords moved normally. On barium swallow there was considerable delay in the œsophagus, caused by external pressure from the aneurysm (Fig. 4) whose right border showed slight pulsation. She received 20 mega units of penicillin. (Herxheimer reaction occurred.)

Progress. One year later she was able to swallow anything and had gained 2 stone, but despite this her dyspnœa was less. Strict dieting started. In June 1957 barium swallow did not show any delay, the aneurysm was no larger and no pulsation was visible. In September 1957 she was leading a fairly normal life and able to go to a neighbouring holiday resort for day excursions, having reduced her weight by 1½ stone. No change at time of writing.

Discussion

We believe from our admittedly small experience that penicillin relieves many of the symptoms of patients suffering from syphilitic aortic aneurysm. The improvement in the general condition of the patients and the gain in weight noted in several cases bears out the assumption of Curtis *et al.* (1951) that occult lesions are present elsewhere than in the cardiovascular system in these cases. The *Treponema pallidum* is extremely sensitive to the action of penicillin and true resistance to this antibiotic does not develop (Beerman *et al.*, 1950). It is probable that the disappearance of syphilitic granulation tissue from the aorta takes many months and that little happens to the lesions during actual treatment. Sinclair *et al.* (1954), reviewing the histology of patients dying following treatment with penicillin for cardiovascular syphilis, although not stating the causes of death, found that in those treated up to four weeks before death there were severe inflammatory changes present in the aortic wall. In those dying ten weeks or longer after treatment there was a marked decrease in or absence of lymphocytic or plasma cell infiltration. In agreement with these findings it is our experience clinically that relief of pain, when present, occurred in under six weeks, but that there was a continued improvement in the general condition of the patient for many months, even up to one year, after the completion of treatment. As regards the hæmoptyses, it is difficult to understand why penicillin therapy should lead to their cessation. These were a leading symptom in three cases. In Case 1 during treatment a hæmoptysis of almost 1 pint occurred. He survived for 20 months despite this and it was thought that the blood had come from the aneurysm via the left main bronchus. In two other cases it was merely staining of the sputum and believed to be in some way due to pressure from the aneurysm on the bronchial wall.

Penicillin has thus been shown to have a marked effect on the *Treponema*

pallidum and syphilitic granulation tissue. It would appear to us that this beneficial effect may mitigate against rupture of the aneurysmal wall.

It is probable that many saccular aneurysms are present a long time before, by reason of their pressure effects, they become evident. The prognosis may, therefore, not be quite as gloomy as is generally supposed. Nevertheless it is certainly bad and, despite the ingenious means devised by our surgical colleagues, operation, often in an elderly subject, is extremely hazardous. It appears to us, therefore, that surgery will have no further part to play in the treatment of this condition and that in many cases penicillin will relieve symptoms and improve the prognosis.

Summary

Thirteen cases of syphilitic aortic aneurysm have been treated with penicillin. All had, on diagnosis, definite symptoms which suggested that death might occur within one or two years. Nine patients are leading reasonably normal lives, having been observed for varying periods between 32 and 74 months.

REFERENCES

Bahnson, H. T. (1953): *Surg. Gynec. Obstet.*, **96,** 383.
Beerman, H., Nicholas, L., Buerk, M. S., and Ford, W. T. (1950): *Arch. Int. Med.*, **85,** 305.
Borrie, J., Griffen, S. G. (1950): *Thorax*, **5,** 293.
Curtis, A. C., Kitchen, D. K., O'Leary, P. A., Rattner, H., Rein, C. R., Schoch, A., Shaffer, L., and Wile, U. (1951): *J. Amer. Med. Ass.*, **145,** 1223.
Grimble, A. (1955): *Guy's Hosp. Rep.*, **104,** 239.
Kampmeier, R. H. (1938): *Ann. Int. Med.*, **12,** 624.
Lancet, leading article (1954): **2,** 1268.
Moore, J. E. (1949): *Amer. J. Syph.*, **33,** 43.
O'Brien, J. F., Smith, C. A., and Fishkeller, M. A. (1955): *Brit. J. ven. Dis.*, **31,** 74.
Sheldon, W., Heyman, A., and Evans, L. (1952): *Amer. J. Syph.*, **36,** 77.
Sinclair, H. A., and Webster, B. (1954): *Amer. J. Syph.*, **38,** 54.

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PULMONARY BULLÆ AND INFECTION

By B. Golberg

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Emphysematous bullæ can be associated with pulmonary infections in three ways. They may develop during acute infections, they may result from the healing of tuberculous disease, and established emphysematous bullæ may become secondarily infected by pyogenic organisms or tubercle bacilli. As an acute occurrence pulmonary emphysema was a prominent pathological finding in the influenza pandemic of 1918-19 (Torrey and Grosh, 1919) and was frequently found in children with pneumonia in the pre-antibiotic era. De Martini (1947) gave a full description of the syndrome in adults in the course of acute or subacute bronchopneumonia. Ravazzoni and Scarponi (1955) reviewed the literature and discussed the aetio-pathogenesis of this condition. At present when bullæ are found in the course of an acute pulmonary infection the causative organism is often the *Staphylococcus aureus* and usually is part of an overt septicæmia or pyæmia. In such cases, or where the bullæ occur in the course of pneumonias due to other organisms, adequate treatment with appropriate antibiotics results in the disappearance of the bullæ at the same time as resolution of the pulmonary lesion. In some, however, there is a lag in the shrinking of the bullæ, and several months may elapse before they disappear. In a few the bullous changes are permanent.

Various types of emphysema of compensatory or obstructive character were a natural consequence of healing in the course of pulmonary tuberculosis in the pre-antibiotic era, and are still found to a lesser extent now. These have been classified by Torelli and de Chiara (1956) as bullous emphysema in fibrotic tuberculous disease, small bullous emphysema in miliary and nodular tuberculosis, in primary tuberculosis, in tuberculous bronchiectasis, as open healed cavities, and as a result of antibacterial treatment. Open cavity healing was noted as a natural occurrence by Laennec. Prior to the advent of antituberculous chemotherapy giant bullous emphysema had been described by Dobric (1938) as a consequence of healing following chrysotherapy, and later by Dufourt *et al.* (1952) in the course of pneumothorax therapy. Since the effective use of antituberculous chemotherapy the development of thin-walled bullous or cystic spaces has been frequently reported and has generally followed treatment of advanced caseous pneumonic or cavernous disease (Alarçon, 1955; Bernou and Brun, 1955). Although these changes characteristically occur after isoniazide therapy, Dufourt *et al.* (1950) found them to occur with streptomycin before the advent of isoniazide. Alarçon (1955) has given a very full review of the main features of this condition and the theories concerning

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its pathogenesis. Rappaport (1955) suggests that inflammatory processes may damage the alveolar walls in the affected areas, causing their apparent disintegration and absorption. Chemotherapy favours more complete self-cleansing of the affected area and prevents the development of dense fibrotic residues. Normal thoracic traction acting upon such defective air spaces, lacking adequate partitioning function by the parenchyma, will overdistend these to the point of failing elastic recoil. This process leads secondarily to check-valve bronchial obstruction and reversible hyperinflation of the already abnormal air spaces. Such spaces predispose to complicating infections, which lead to secondary bronchial obstruction and its sequelæ. Incomplete obstruction will exaggerate the air space abnormality, complete obstruction accounts for reversal or occasional disappearance of abnormal air spaces.

Case 1. F.B.T., a 53-year-old sawyer, was treated for extensive pulmonary tuberculosis and spinal caries from March 1952 until December 1953, receiving streptomycin, PAS and isoniazide usually in combination, except for a four-month period on 400 mg. isoniazide daily on its own. The results were good, but bullous changes of moderate extent were present in the left upper zone. Gradual enlargement of the bullæ occurred between December 1954 and April 1956 necessitating open cavity drainage because of his poor general condition. Although he has remained well since then, there has been slight re-expansion of the bulla.

Case 2. F.K., a 51-year-old female cook, was treated for very gross pulmonary tuberculosis (Fig. 1) from May 1952 until December 1953. She received streptomycin, PAS and INAH 400 mg. daily in various combinations for seven months and made an excellent recovery. However, her condition deteriorated over the ensuing years, and in July 1955 (Fig. 2) chemotherapy was restarted and has been continued until the present. She again made good progress, but this time developed systems of thin-walled bullous spaces at both upper zones which enlarged over a period of months, and then remained static (Fig. 3). She had always been subject to bronchitis, and in April 1957 she suffered an unusually severe attack, with profuse greenish sputum which grew *Staphylococcus aureus* on culture. Her X-ray showed filling up of the bullæ on the left (Fig. 4). With penicillin her acute symptoms cleared and the left upper zone bullæ have remained closed.

These two cases demonstrate the evolution of thin-walled bullæ or cavities at the site of extensive caseous and cavitary disease following chemotherapy. In one of them progressive distension, probably due to check-valve bronchial obstruction, necessitated cavity drainage. In the other superadded infection resulted in closure of the spaces on one side, probably by causing complete bronchial obstruction.

While resolution of tuberculous processes leading to vanishing lung areas is now a common observation, the invasion of emphysematous bullous spaces by tuberculous disease is a less frequent, but equally striking, event. Rothstein (1954) has described eight such cases. In these the bullous walls and septa were characteristically involved, with the development of fluid levels within the bullæ. The ensuing bizarre appearances are typical of the condition, but,

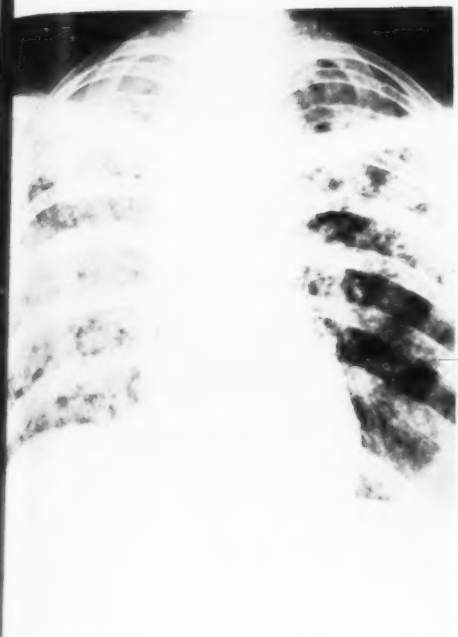

FIG. 1.—Case 2. Radiograph of May 1952 showing extensive fibrocaseous tuberculosis prior to treatment.

FIG. 2.—Case 2. Radiograph of July 1955 following relapse showing bilateral upper zone cavities.

FIG. 3.—Case 2. Radiograph of July 1956 after a year's continuous chemotherapy. Bullous changes are present in both upper zones.

FIG. 4.—Case 2. Radiograph of April 1957. The bulla on the left has obliterated after an acute respiratory infection.

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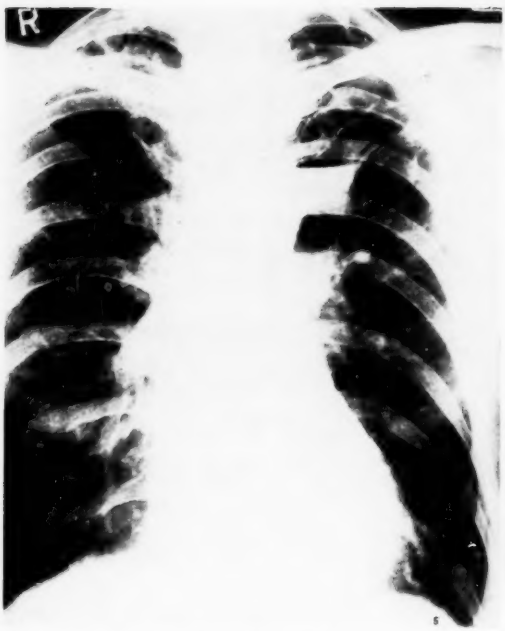

FIG. 5.—Case 5. Radiograph of February 1955 during a febrile respiratory illness showing bullae with a fluid level in the left upper zone.

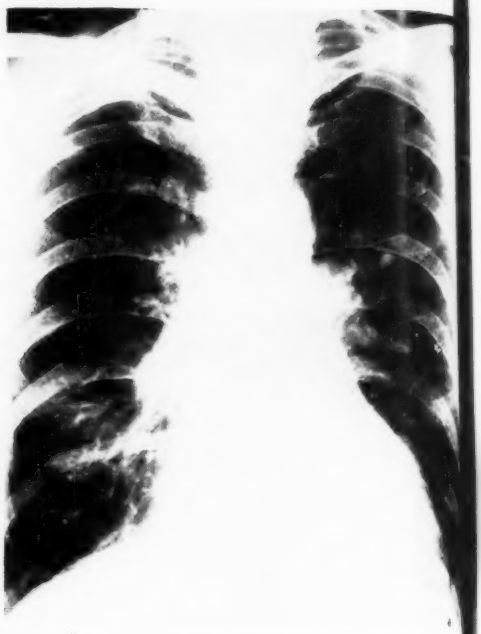

FIG. 6.—Case 5. Radiograph of March 1955 after recovery. The fluid has disappeared, but the bullae remain unchanged.

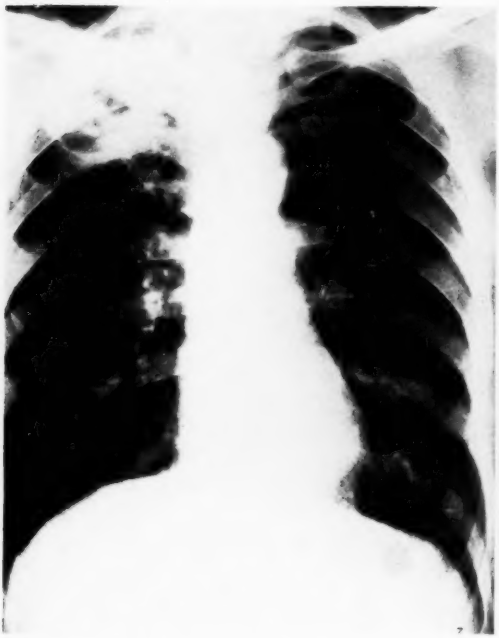

FIG. 7.—Case 6. Radiograph of May 1956 showing acutely infected bullous spaces.

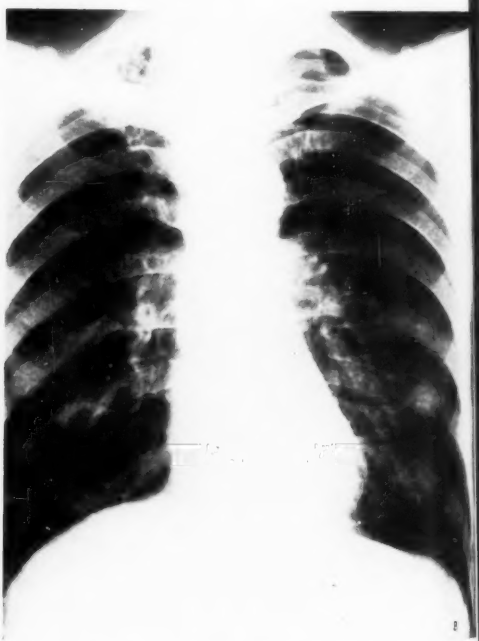

FIG. 8.—Case 6. Radiograph of January 1958. Only little fibrotic streaking remains at the right apex.

if not recognised, may suggest multiple extensive cavitation or abscesses. In all the development of the inflammatory changes and fluid levels was asymptomatic, and was usually followed by gradual shrinkage and obliteration of the bullæ, leaving fibrotic scarring. These patients all responded to normal antituberculous measures. The author has described a further case (Golberg, 1956) in which the fatal outcome was in contrast to the previously reported favourable results and was undoubtedly due to the extent and severity of the changes present.

CASE 3. A schoolgirl, B.J.B., aged 13, was under supervision at the Ashford Chest Clinic from March to September 1955 suffering from recurrent attacks of asthma. Her X-ray showed only slightly emphysematous lung fields. Between September and December she had had a succession of colds and had lost weight. X-ray in December showed a system of spaces occupying much of the right upper lobe. It was thought that she might have a staphylococcal pneumonia and she was admitted to Ashford Hospital. Investigations revealed pneumococci and hæmophilus in her sputum, Mantoux was positive to 1 : 100 O.T. Bronchograms showed adequate filling of all the right bronchial tree except for the posterior branch of the right upper lobe. It was felt that the lesion was an obstructive one, due to infection, and she was treated with oral tetracycline and "Alevaire" inhalations. Her general condition began to improve, but the bullæ actually continued to increase in size. She was then given a month's course of prednisone and penicillin, during which her clinical improvement continued but without any radiological change. At this stage surgical measures were suggested, but the patient and her parents were anxious to try conservative treatment for a little longer and she was discharged to continue under observation as an out-patient. Soon after her discharge her sputum, which had been repeatedly negative for tubercle bacilli, was found to be positive on direct examination. Her X-ray showed a fluid level in the bullæ, and it seemed likely that the bullæ had now undergone a tuberculous infection, probably the result of the prednisone.

The advent of a fluid level and tuberculous infection should have been the harbinger of healing and closure of the bullæ, but this did not prove to be the case. Treatment was started with streptomycin and isoniazide, and initially the bullæ decreased in size for the first time. This improvement did not continue, however, and she was transferred to a thoracic surgical centre for surgery to be considered. Right upper lobectomy was eventually performed on 4.2.57, the cysts having gradually continued to enlarge. At operation a large tense cyst was found, almost completely replacing the right upper lobe, and bound down by widespread pleural adhesions. The wall was generally smooth and trabeculated but granular in some areas, up to 8 mm. in thickness, and bathed in a thin greenish pus. A partly cavitated caseous focus 1·5 cm. in diameter was present near the hilar area, and there were also a number of calcified lymph glands. The pathologist felt that the cyst was definitely a pulmonary cavity.

The pathogenesis of this lesion could be accounted for in two ways—it may have been a tuberculous cavity *ab initio*, or, as seemed more likely, initially an acutely developing emphysematous bulla associated with acute bronchopneumonia, followed by secondary infection by tubercle bacilli during a course of corticosteroid therapy. Unlike most previously described cases, the bullæ

did not improve with antituberculous therapy and eventually had to be excised. The patient did well after operation and was discharged 16.6.57.

Considering the frequency with which bullous emphysema is found, often in patients with chronic bronchitis and subject to repeated respiratory infections, it is surprising how rarely acute pyogenic infection of the bullous areas takes place. I have been able to find only five publications on the subject, dealing with seven cases in all (Rothstein, 1954; Benda and Franchel, 1951; Roques *et al.*, 1946; Rigler, 1946; Weisel and Slotnik, 1950). Unlike the cases where tuberculous infection occurs, these patients have definite symptoms of acute respiratory infection. The X-ray appearances may suggest multiple cavitation or abscess formation.

The clinical picture and course is generally benign, with satisfactory response to appropriate antibiotic treatment.

Case 4. V.E.A., a 49-year-old precision tool grinder, had had asthma all his life. X-ray in 1955 showed widespread emphysematous bullous changes in both lungs. In April 1957 he became acutely ill with a pleuritic type of pain on the left side of his chest. After three weeks' rest in bed he attended the clinic 25.4.57 feeling very much better. X-ray showed numerous fluid levels in his left lung. Sputum grew pneumococci on culture, W.B.C. 23,000. He was treated with penicillin and in a month felt remarkably fit. He had lost his life-long wheeze and has remained very much better ever since. Serial X-rays have shown shrinking of the bullæ in the left upper zone.

Sometimes the bullæ are discovered only because symptoms resulting from their infection make the patient seek medical advice.

Case 5. S.W.T., a 54-year-old male cashier, complained of bronchitis for two years. Two weeks before his attendance at the clinic he developed a troublesome cough with an increase in sputum and rigors. His X-ray (Fig. 5) showed a system of bullous cavities in the left upper zone with a fluid level. He improved without treatment, the fluid clearing, but the bullæ have remained unchanged (Fig. 6).

Case 6. T.Y.W., a 55-year-old male, was seen at the clinic in May 1956 with what appeared to be infiltration and cavitation with a fluid level at the right apex (Fig. 7). After two weeks of antituberculous chemotherapy it was found that all his sputa were negative for tubercle bacilli and the treatment was stopped. Bronchoscopy and sputum examination for neoplastic cells were negative. He was given a prolonged course of penicillin with rapid improvement. On discharge the lesion had shrunk very considerably and his recent film shows only slight fibrotic changes (Fig. 8). This must have been a case of pyogenic infection of pre-existing bullæ.

The various means by which emphysematous bullous changes develop in the course of healing in tuberculosis have been already discussed. Spaces which have developed in this manner are not spared subsequent acute pyogenic infections.

CASE 7. R.C., a 50-year-old male, was found to have calcified hilar glands with limited bullous changes at the right apex in November 1945. He remained under observation with very gradual increase in the size of the bullæ over the years. In August 1957 he became acutely ill with a respiratory infection. X-ray showed consolidation of the right upper lobe with a fluid level in the bulla. A ten-day course of tetracycline was given with clinical recovery. His most recent X-ray shows almost complete closure of the bulla.

It will be seen from the cases demonstrated that infection of emphysematous bullæ, either by pyogenic organisms or by tubercle bacilli, is not as infrequent as might be thought from the scanty literature on the subject. Recognition of the true aetiology in such a case will save the physician a great deal of anxiety and will sometimes spare the patient unnecessary and potentially harmful operative interference, as these cases are not infrequently diagnosed as empyemata and subjected to rib resection. In the majority adequate conservative treatment will result in satisfactory resolution and it is only in a small minority that surgical measures—either cavity drainage or resection—are required. These measures can usually be carried out at a time of election and not as an emergency.

Summary

The relationship between emphysematous bullæ and pulmonary infection is discussed. Seven cases are described which illustrate the development and regression of bullæ associated with tuberculous and acute pyogenic infections.

REFERENCES

ALARCON, D. G. (1955): *Dis. Chest.*, **27,** 31.
BENDA, R., and FRANCHEL, F. (1951): *Bull. Soc. méd. Hôp. Paris*, **67,** 1058.
BERNOU, A., and BRUN. J. (1955): *Presse Méd.*, **63,** 894.
DE MARTINI, A. (1947): *Minerva Med. (Torino)*, **39,** 276.
DOBRIC, L. L. (1938): *Rev. tuberc. Urug.*, **7,** 98.
DUFOURT, A., GALY, P., and PERRIN, J. (1950): *J. franç. Méd. Chir. thorac.*, **4,** 157.
DUFOURT, A., BRUN, J., and VIALLER (1952): *Rev. Tuberc.*, **16,** 635.
GOLBERG, B. (1956): *Brit. J. Tuberc. and Dis. Chest*, **50,** 362.
PEIRCE, C. B., and DIRKSE, P. R. (1937): *J. Radiology*, **28,** 651.
RAPPAPORT, I. (1955): *J. Amer. med. Ass.*, **158,** 1436.
RAVAZZONI, C., and SCARPONI, F. (1955): *Arch. Maragliano pat. clin.*, **10,** 1055.
RIGLER, L. G. (1946): "The Chest," p. 168. Year Book Publishers, Chicago, Ill.
ROQUES, E., DE BRUX, J., and BOLLINELLI, R. (1946): *Bull. Soc. méd. Hôp. Paris*, **62,** 125.
ROTHSTEIN, E. (1954): *Amer. Rev. Tuberc.*, **69,** 287.
TORELLI, G., and CHIARA, C. DE (1956): *Minerva Med. (Torino)*, **47,** 1776.
TORREY, R. G., and GROSH, L. C. (1919): *Amer. J. med. Sci.*, **157,** 170.
WEISEL, W., and SLOTNIK, I. (1950): *Amer. Rev. Tuberc.*, **61,** 742.

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PLASMACYTOMA OF LUNG AND STOMACH

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Extra-medullary plasma cell tumours are relatively uncommon but distinctive neoplasms. Since the first description by Schridde (1905) of a plasmacytoma of the nasal cavity this tumour has been reported with increasing frequency. The upper respiratory tract is the site of election. Hellwig (1943) in a review of 127 published cases found 63 tumours arising in this situation. Other primary sites included the pleura, mediastinum, ovary, thyroid, kidney, lachrymal gland, intestine, stomach, lymph nodes, spermatic cord and the skin. The conjunctiva was the site of origin in forty-seven cases, but these lesions are rarely invasive and many are probably of inflammatory origin. A primary origin in the lung is very rare although a few convincing cases are on record. Secondary deposits in the lung are also very uncommon even when wide dissemination has taken place. Stout and Kenney (1949) found no instances of lung secondaries in 107 cases of upper respiratory plasmacytoma. The stomach is a relatively uncommon site for this tumour and reference to only one example is made in Hellwig's review (1943). Some nine cases are now on record (Hampton and Gandy, 1957).

In the case here reported plasma cell tumours of the stomach and lung were present and characteristic plasma protein abnormalities were demonstrated by electrophoresis. Involvement of the bone marrow occurred only as a terminal event.

Case Report

In November 1955 Mrs. G., a married woman of German origin, aged 48 years, complained of cough producing a little sputum, night sweats, effort dyspnœa and right chest pain. An operation had been performed in 1951 for dysmenorrhœa associated with hydrosalpinx and ovarian cysts. Her previous health had otherwise been excellent. A chest radiograph in December 1955 revealed a triangular opacity in the right lower zone involving the lower lobe. In January 1956 she was admitted to the Whittington Hospital. On examination her general condition was good, she had a temperature of 99° F. (37·2° C.) and the air entry was diminished over the right lower zone posteriorly. An E.S.R. was 50 mm./hr. Sputum examinations failed to demonstrate tubercle bacilli or malignant cells. The appearances at bronchoscopy were normal. There was an initial increase in the size of the lesion radiographically, in spite of a course of Crystamycin and tetracycline. Pulmonary tuberculosis was considered the most likely diagnosis and the patient was discharged home on anti-tuberculous drugs. On discharge she was afebrile and had gained 4 lb. in weight.

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In May 1956 the patient was admitted to the Middlesex Hospital in view of the persistence of symptoms; she was afebrile on admission but signs of consolidation were present in the right lower chest. There were no other abnormal signs.

Investigations

Chest radiograph (Fig. 1)* showed an irregular opacity involving the apical and posterior basal segments of the right lower lobe. Hæmoglobin 10·3 g. %. Total leucocyte count 11,100 per c.mm. (neutrophils 83%, lymphocytes 13%, monocytes 3% and eosinophils 1%), E.S.R. (Wintrobe) 33 mm./hr. Sputum cultures and smears were repeatedly negative for tubercle bacilli. Mantoux reaction 1/1,000 positive. W.R. negative. Total plasma proteins 7·2 g. %, albumin 4·0 g. %, globulin 3·2 g. %. Liver function tests were normal. Bronchoscopy showed no abnormality. A bronchogram revealed some crowding of the right basal bronchi.

On June 20, 1956, an exploratory right posterior thoracotomy was performed by Mr. J. R. Belcher. The entire lower lobe and part of the middle and upper lobes were found to be replaced by soft grey gelatinous tissue adherent to the hilum and to the œsophagus and pericardium. Frozen sections of biopsy material showed no evidence of tumour and the wound was therefore closed after further generous biopsies had been taken.

Histology

" Sections show a granulomatous lesion consisting of proliferating fibroblasts, histiocytes, reticulum cells and numerous plasma cells. Some foam cell areas are present.

No bacteria or fungi were seen and all cultures were sterile. The appearances favour an inflammatory origin, but plasmacytoma should be considered."

Post-operatively, the patient was treated with tetracycline, cortisone and potassium iodide without effect. There was no significant change in the lung lesion at the time of discharge on August 31, 1956.

In November 1956 she was admitted again complaining of persistent chest pain and increasing dyspnœa. The lung lesion had increased somewhat in size with evidence of considerable pleural involvement.

Investigations

Hæmoglobin 12·9 g. %. Total leucocyte count 8,800 per c. mm., differential count normal. Plasma proteins 5·7 g. %, albumin 3·1 g. %, globulin 2·6 g. %; serum electrophoresis showed a raised α_2 globulin and an abnormal band of specific mobility in the γ globulin, compatible with myelomatosis (Fig. 3). There was no other evidence of myelomatosis. Skeletal X-rays were normal. Serum calcium 9·0 mg. %. The urine contained no protein or proteose. An iliac crest puncture yielded normal bone marrow.

In view of the increasing size of the lesion and its possibly neoplastic nature, a course of deep X-ray therapy was given. Treatment was given by anterior and posterior grid fields to a tumour dose of 3,540 r. in 23 treatments spread over 32 days. Some symptomatic improvement and decrease in size of the lesion took place and the patient was discharged on December 11, 1956.

* Figures referred to in the text appear on Plates XII-XIII.

From the time of discharge until readmission in March 1957 she complained of increasingly severe epigastric pain and occasional vomiting. The pain was unrelated to meals. Her appetite was very poor and she had lost half a stone in weight. On examination there was some tenderness in the upper abdomen but no other significant finding. A barium meal showed loss of normal mucosal pattern and a filling defect on the greater curve of the stomach (Fig. 2). The appearances favoured extensive neoplastic invasion of the stomach. This diagnosis was confirmed at gastroscopy when the mucosa appeared nodular and extensively infiltrated by tumour; no ulceration was seen, but exudate partly covered the surface of the growth and altered blood was present in the stomach. Serum electrophoresis again showed a myeloma pattern (albumin 3·4 g. %, globulin 2·8 g. %).

On April 9, 1957, laparotomy was performed by Mr. R. S. Handley. The stomach was found to be diffusely invaded by white tumour extending into the mesocolon. Many invaded glands were present around the left gastric artery and cœliac axis. The liver and spleen appeared normal. No peritoneal deposits were seen. In view of the extensive spread of the tumour radical excision was not possible. A palliative total gastrectomy was, therefore, performed.

Pathological Findings

Gross appearance: " Total gastrectomy with 1 in. duodenum and portions of greater and lesser omenta. There is diffuse thickening of the stomach most marked on the greater curve, where the wall is replaced by firm white tissue extending into the greater omentum to form a mass measuring 1 in. × 4in. × 4½ in. The fundus shows minimal involvement. The mucosal surface presents a nodular appearance with complete loss of normal pattern and small areas of superficial ulceration. Enlarged lymph nodes measuring up to ¾ in. diameter are present along the lesser curve. On section the nodes are firm and of homogeneous white appearance." (Fig. 5.)

Histology

" *Plasmacytoma of stomach.* Sections show invasion of all coats of stomach by a tumour composed of plasma cells. In some areas the cells are atypical and numerous Russel bodies are present. Mitoses are scanty. The duodenal cuff is free from invasion, but on the lesser curve tumour extends to the upper limit of excision. The glands sectioned are extensively invaded." (Figs. 7A and B.)

Following operation the patient made a slow but uneventful recovery and was discharged on May 7, 1957. Sternal puncture (26.4.57) again showed normal bone marrow. Electrophoresis of serum proteins one month after operation showed complete disappearance of the myeloma-type γ globulin (Fig. 4).

Following discharge, the patient deteriorated slowly with steady loss of weight and an increase of cough and sputum. She was readmitted to hospital on June 15, 1958, with a story of pain of pleuritic character in the left chest and hæmoptysis. On examination there were signs of fibrosis of the right lung and of consolidation in the left lower lobe. There were no other signs of recurrence. A chest radiograph showed a shrunken right lung and a mass lying in the left lower lobe.

The hæmoglobin was 9·6 g. %, total leucocyte count 13,800 per c. mm. A sternal marrow biopsy (2.7.58) showed an increase of plasma cells (13·4 %),

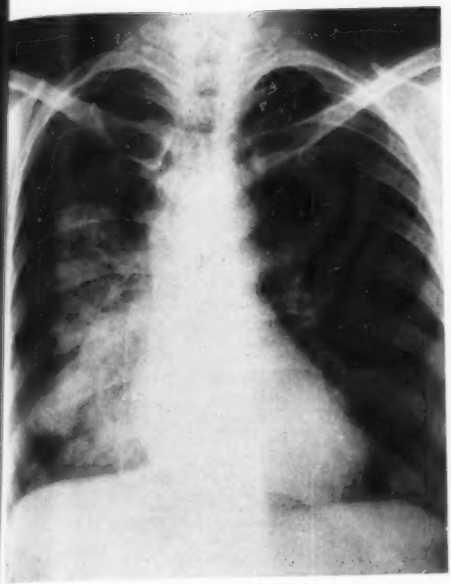

FIG. 1.—Chest radiograph (18.6.56) showing the extent of the pulmonary lesion before deep X-ray therapy.

FIG. 2.—Barium meal (22.3.57) showing the filling defect on the greater curvature of the stomach.

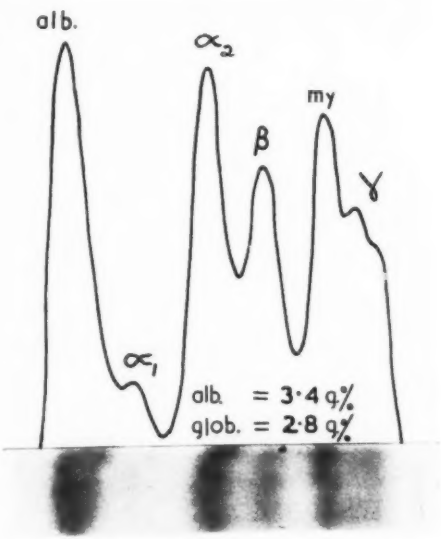

FIG. 3.—Electrophoretic pattern showing the abnormal band of specific mobility (my).

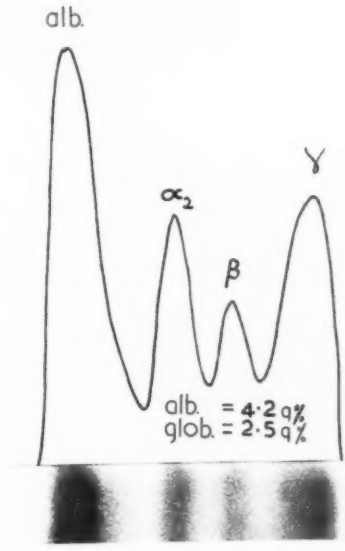

FIG. 4.—Electrophoretic pattern following gastrectomy showing the absence of the specific band (my).

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FIG. 5.—Gastrectomy specimen showing diffuse invasion of the stomach wall and extension of tumour into the greater omentum.

FIG. 6.—Showing the fibrotic, contracted right lung and a tumour mass in the left lower lobe.

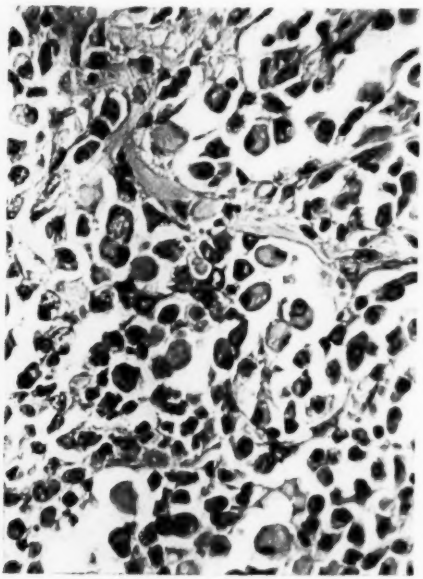

FIG. 7(a).—Section of the stomach showing typical plasma cells. (×380).

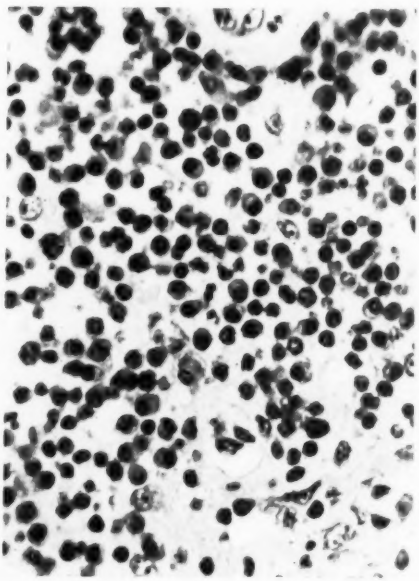

FIG. 7(b).—A section from another area of the gastric tumour showing grossly abnormal plasma cells. (×380).

compatible with multiple myelomatosis. No abnormal band was seen in the electrophoretic strip.

The patient's condition rapidly worsened, she developed a chest infection and despite treatment died suddenly on July 17, 1958, following a severe bout of coughing.

Post-mortem Findings

Thorax. The right pleural cavity was largely obliterated by dense adhesions. An empyema cavity containing yellow pus was present over the lower lobe. The right lung was grossly fibrotic and contracted with displacement of the mediastinum. Scattered areas of abscess formation and broncho-pneumonia were present. No obvious remaining tumour was seen. The left lung showed a deposit of white tumour 3 in. diameter in the lower lobe. The remainder of the lung was congested and œdematous. The hilar lymph nodes were moderately enlarged. Cultures from both lungs and the empyema yielded *Staph. pyogenes.*

Histology. Sections of the left lower lobe and hilar lymph nodes showed invasion by plasmacytoma resembling the gastric tumour. The right lung showed extensive inflammatory changes, but some areas of unequivocal plasmacytoma were also seen. (Fig. 6.)

Abdomen. A total gastrectomy had been performed. A mass of white tumour 1½ in. diameter was present on the outer surface of the œsophageal anastomosis. The iliac, para-aortic, cœliac and supra-pancreatic lymph nodes were moderately enlarged. There were no other significant macroscopic abnormalities.

Histology. Sections of the œsophageal mass and lymph nodes showed invasion by plasmacytoma. The liver was not invaded. There was diffuse infiltration of the splenic pulp by abnormal plasma cells, but the follicular pattern was preserved.

Bones. No macroscopic lesions were seen in the bones. The red marrow of the femur extended for two-thirds of the shaft.

Histology. Sections of femur, sternum, vertebræ and ribs showed diffuse infiltration of the marrow by abnormal plasma cells. Focal lesions were not seen.

Head. No abnormality was seen in the skull, brain or meninges.

Discussion

The main problem presented by this case was to establish the nature of the pulmonary lesion. At thoracotomy the appearance was that of a neoplasm extensively invading the lung. In contrast to this striking macroscopic appearance the histology of the biopsy was not diagnostic. Although numerous plasma cells were present the overall structure favoured an inflammatory process rather than a neoplasm. Serum electrophoresis demonstrated an abnormal gamma-globulin seen in myelomatosis, lending support to a diagnosis of plasmacytoma, but the extreme rarity of these tumours in the lung and the equivocal histology discouraged the diagnosis.

It is well recognised that considerable structural variation of plasma cell tumours occurs and distinction from inflammatory processes may be difficult

(Hellwig, 1943). This variation is seen not only between separate deposits but also within an individual tumour. For this reason biopsy material may not be representative. The rarity of pulmonary plasma cell tumours suggests that the lung offers an unfavourable environment for growth, and this may itself influence their structure. Superadded inflammatory changes readily occur in the lung, serving to complicate the histological diagnosis even more.

Seven previously reported tumours have shown a wide range of microscopic structure. Gordon and Walker (1944) and Hill and White (1953) reported tumours with fairly distinct neoplastic characters. Childress and Adie (1950) described a plasmacytoma of the lung with numerous Russel bodies but showing also some granulomatous features. The lesion described by Cotton and Penido (1952), although diagnosed as neoplastic, was of decidedly granulomatous structure, with considerable fibrosis and relatively few plasma cells. Kuley and Kuntman (1951) reported a plasmacytoma of lung, but based the diagnosis on smears of aspirated cells alone. The histological structure was, therefore, not established. Rozsa and Fireman (1953) reported two cases, but gave little detail of the histological appearances within the lung.

Little is known regarding the behaviour of these tumours in the lung. The development of multiple myeloma many years after the removal of an apparently isolated extra-medullary plasmacytoma is well recognised and such a relationship may exist with the lung tumours. The patient reported by Hill and White (1955) was alive and well eight years after removal of the tumour, but even this period is not adequate to ensure that dissemination will not occur.

The tendency to a granulomatous structure which the pulmonary tumours may exhibit suggests that their neoplastic nature may sometimes remain unrecognised. The possibility of plasmacytoma should be considered whenever an apparently granulomatous lesion of obscure ætiology is found in the lung. Lane *et al.* (1955) described a case of " plasma cell granuloma " of the lung. No evidence of myelomatosis was found and the lesion was regarded as inflammatory in origin. Long-term follow-up of such cases would be of interest.

In contrast to the equivocal appearance of the lung biopsy the histology of the gastric tumour was characteristic. All transitions between normal and grossly atypical plasma cells were present and the malignant nature was clearly indicated by extensive invasion of stomach, omentum and lymph nodes. Similar tumour was present in both lungs at autopsy. The relationship of the gastric and pulmonary tumours is a matter of conjecture. The clinical history gave little indication of their relative duration. The behaviour of plasma cell tumours suggests that a multicentric origin as well as metastasis may occur and it is possible that the two tumours represent independent foci of formation.

A remarkable feature of this case was the presence of myeloma globulin in the serum and its complete disappearance following total gastrectomy. Bence Jones proteose was absent from the urine. This proteose is usually associated with bony involvement which in this patient only occurred shortly before death.

Summary

A case of plasma cell tumours of the lung and stomach is described. Myeloma globulin was present in the serum and disappeared completely following total gastrectomy. Involvement of the bone marrow occurred only as a terminal event. It is suggested that the possibility of plasmacytoma should be considered whenever an apparently granulomatous lesion of obscure ætiology is encountered in the lung.

We wish to thank Dr. F. H. Scadding, under whose care the patient was admitted, for allowing us to publish this case.

REFERENCES

CHILDRESS, W. G., and ADIE, G. C. (1950): *J. thorac. Surg.*, **19,** 794.
(1955): *ibid.*, **29,** 480.
COTTON, B. H., and PENIDO, J. R. F. (1952): *Dis. Chest.*, **21,** 218.
GORDON, J., and WALKER, G. (1944): *Arch. Path.*, **37,** 222.
HAMPTON, J. M., and GANDY, J. R. (1957): *Ann. Surg.*, **145,** 415.
HELLWIG, C. A. (1943): *Arch. Path.*, **36,** 95.
HILL, L. D., and WHITE, M. L. (1953): *J. thorac. Surg.*, **25,** 187.
KULEY, M., and KUNTMAN, O. (1951): *Dis. Chest.*, **19,** 227.
LANE, I. D., KROHN, S., KOLOZSI, W., and WHITEHEAD, R. E. (1955): *Dis. Chest.*, **27,** 216.
ROZSA, S., and FIREMAN, H. (1953): *Amer. J. Roentgenol.*, **70,** 982.
SCHRIDDE, H. (1905): *Zbl. allg. Path. path. Anat.*, **16,** 433.
STOUT, P. S., and KENNEY, F. R. (1949): *Cancer*, **2,** 261.

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THE ERYTHROCYTE SEDIMENTATION RATE IN PLASMA DETERGENT MIXTURES

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The inter-relationship between the mass of the different protein fractions in the blood plasma, and the rate at which the erythrocytes settle in the plasma (the erythrocyte sedimentation rate), was demonstrated by Fahreus (1921). Fibrinogen was shown to have the greatest and albumin the smallest effect on the rate. The variation in the erythrocyte sedimentation rate (E.S.R.) is governed by the size of the aggregate formed by the clumping together of the rouleaux of red blood cells, the aggregate size being constant for a particular plasma.

Advances in the technique of plasma analysis, first by salt fractionation methods, and more recently by electrophoresis, have led to attempts to obtain a mathematical relationship between the mass of the various proteins present in the plasma and the E.S.R. (Meyer *et al.*, 1953). These attempts have had little success, one possible reason being that analytical techniques are still not sufficiently accurate to ensure a critical separation of all the protein fractions present in the plasma. By means of synthetic plasmas Hardwicke and Squires (1952) were able to obtain a mathematical relationship between the maximum velocity of fall of the erythrocytes and the concentration of the macromolecules. They were, however, unable to apply this formula to natural plasma.

Sykes (1948) drew attention to a finding of Schutt (1928) that the addition of very small amounts of ether to plasma caused an increase in the E.S.R., whereas addition of a larger amount resulted in a slower rate. Since that time, however, with the advent of the detergents, a more potent method of effecting changes in the chemical and physico-chemical properties of protein has been found. Addition of minute quantities of detergent to a protein solution will bring about profound changes in the protein (Anson and Edsall, 1948).

The present paper is based on experiments performed on blood from a series of tuberculous patients with raised E.S.R.s to determine what effect the modification in the plasma proteins by addition of detergent would have on the E.S.R. For the purpose of these experiments a cationic detergent, cetyl trimethyl ammonium bromide (cetavlon), was used. The anionic detergents were found to be less effective.

Method

Twelve millilitres of blood were aspirated through a wide bore needle into a silicone lubricated syringe with a minimum of venous stasis. Two millilitres of the blood were added to 0·5 millilitre of a 3·8 per cent. solution of sodium

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citrate in each of six tubes. Five of the tubes contained different amounts of cetavlon (see Table 1).

The E.S.R.s for the six citrated bloods were then determined, using the method described by Rourke and Ernstene (1930), and observing precautions against the sources of error described by Ham and Curtis (1938). The results are given in Table 1.

Addition of the detergent to the blood causes a reduction of the E.S.R. until, in the higher concentrations, the rate is similar to that of the individual erythrocyte. Microscopy of the blood at this concentration of detergent reveals that there is no aggregate formation, and that the rouleaux are composed of no more than five to ten erythrocytes.

Plasma Viscosity

Various workers (T'ang and Wang, 1941, Harkness *et al.*, 1946) have shown that increased viscosity of the plasma is associated with an increased E.S.R., and Harkness and his co-workers consider the plasma viscosity a more reliable index of the disease process than the E.S.R.

The viscosities of the various plasma-cetavlon solutions used in the above experiments were determined, using the simple capillary viscometer described by Steele (1948), and following the modifications described by Hardwicke and Squires (1952). The results are given in Table 1.

It will be seen that with increasing amounts of cetavlon there is progressive lowering of the E.S.R., but there is an increase in the plasma viscosity. This is in direct contrast to the normal finding of increased E.S.R. with increased viscosity.

In order to determine if the detergent acts solely on the plasma, or on erythrocytes, or on both these constituents of the blood, a series of experiments was performed in which two samples of two millilitres of blood were taken from each patient and added to 0·5 millilitre of a 3·8 per cent. solution of sodium citrate. Sufficient cetavlon to cause inhibition of the E.S.R. had been added to one of the 0·5 millilitre of sodium citrate solution. The amount of cetavlon required had been previously determined experimentally by the method already described.

The sedimentation rate was determined for the blood plus citrate mixture (sample A), and for the blood plus citrate-cetavlon mixture (sample B). Plasma and cells of both samples were then separated by centrifuging at 3,000 revs./min. for 20 minutes. After repeated washing of the blood corpuscles with normal saline, the cells from sample A were added to the plasma from sample B, and the cells from sample B were added to the plasma from sample A. The reconstituted bloods were then each mixed and the E.S.R.s again determined.

It was found that the E.S.R. in the mixture containing the normal plasma corresponded to the E.S.R. in the normal blood sample (sample A), whereas the sample containing the plasma from the blood-cetavlon mixture (sample B) showed the same inhibition that was found in the original sample B. It was

TABLE 1.—E.S.R. (MAXIMUM VELOCITY) AND RELATIVE VISCOSITY OF PLASMA FOLLOWING ADDITION OF CETAVLON TO CITRATED BLOOD

Amount cetavlon per 2 c.c. blood	*Distance fallen by erythrocytes in mm. measured at 5-minute intervals*																									*Max. vel.*	*Rel. visc.*
mg.	5	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110	115	120		*mm./hr.*	
0	2	4	6	8	11	15	19	24	28	32	36	39	43	47	49	51	54	55	57	59	61	62	64	66		48	1·56
0·1	1	2	3	5	6	7	8	10	11	15	17	19	21	23	24	26	28	29	31	32	33	34	36	38		32	1·61
0·15	0	0	1	1	1	1	1	2	2	3	3	3	4	4	4	5	5	6	6	7	7	7	7	8		5	1·64
0·175	0	0	0	0	0	1	1	1	1	1	1	1	2	2	2	2	2	3	3	3	3	3	3	4		4	1·66
0·2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1		1	1·68
0·225	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1		1	1·68

thus shown that the factor causing inhibition of the E.S.R. when cetavlon is added to blood is confined to the plasma, since both sets of cells behaved normally in the normal plasma, and has no apparent effect on the erythrocytes themselves.

In the various experiments performed with the different samples of plasma, it was found that the amount of detergent required to obtain the maximum effect on the E.S.R. varied within narrow limits (0·175-0·255 mg. per 2 millilitres blood). Addition of further amounts of detergent beyond this amount caused hæmolysis of the erythrocytes.

Surface Tension

Another manifestation of changes in the physical properties of the colloidal solution of plasma proteins is alteration in the surface tension. In most colloidal solutions the addition of detergent causes a sharp drop in the surface tension followed by a gradual rise towards its original value (the Du Nuoy phenomenon). The explanation is thought to be that the detergent first spreads over the solution-air interface, causing the sharp drop in the surface tension, and later, reacting with the colloidal particles, is absorbed on to the surface of the particles, with the result that the surface tension rises.

The surface tension of the plasma cetavlon mixture was measured by the stalagmometer as described by Jirgensons and Straumanis (1954). The method is based on the determination of the work required for the formation of a fresh surface of the liquid in the form of drops. A fixed volume of the liquid is allowed to drop from the lower glass surface of the stalagmometer at the rate of one drop every two to three seconds. The number of drops formed by the fixed volume of fluid is counted, and compared with the number of drops formed by an identical volume of distilled water.

The surface tension is then found by the formula:

$$\text{S.T.} = \frac{73\ Z_w}{Z} \times D$$

Z_w = number of drops of water
Z = number of drops of liquid
D = density of liquid

For the untreated plasma the surface tension was found to be 68 dynes per centimetre. For plasma with added detergent the surface tension was 44 dynes per centimetre. No Du Nuoy phenomenon was observed in the plasma-cetavlon mixture in the concentrations used.

Analysis of the Protein-detergent Mixture

There was no formation of a fibrin clot when calcium chloride solution was added to the plasma-cetavlon mixture. This failure of the plasma-cetavlon mixture to clot may be due to alteration in the fibrinogen, or to modification of the prothrombin. This is now being investigated.

Electrophoresis of Serum Detergent Mixture

Analysis of untreated serum and of serum to which detergent had been added was carried out by paper electrophoresis, using a barbiturate buffer solution of *p*H 8, and staining with azocarmine after the method described by Pluckthun and Gotting (1951). The dyed filter paper strips were then scanned according to the method described by Crook *et al.* (1954). The resultant traces are shown in Fig. 1.

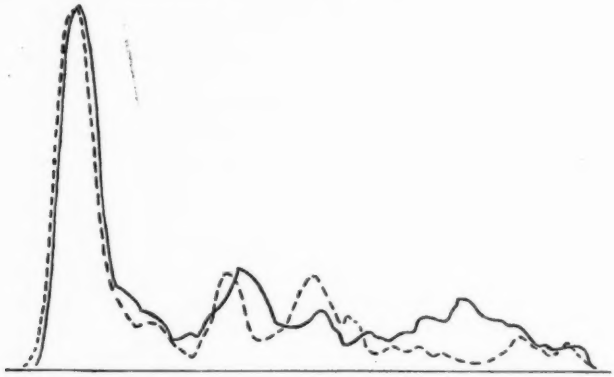

Fig. 1.—Electrophoresis traces of serum and serum—detergent mixtures. Continuous line=serum. Interrupted line=serum+detergent.

These traces show a modification in the gamma globulin as demonstrated by a disappearance of the gamma globulin peak in the serum-detergent trace. At the same time there may be some change in the alpha 2 and beta globulins as shown by the change in size and position of these peaks in the serum-detergent trace.

Discussion

With the addition of small amounts of detergent to protein solutions Putnam and Neurath (1945) were able to show electrophoretically that excess protein migrated as a distinct entity from the protein-detergent complex, suggesting that the whole protein molecule becomes involved in the complex, or remains entirely dissociated from the detergent. The complex appears, therefore, to be formed as the result of a primary chemical reaction.

Viscosity measurements and X-ray diffraction studies as a means of investigating molecular shapes have shown that the detergents bring about an unfolding of the protein molecule, which loses its rigid configuration and assumes a more random orientation. The viscosity of the solution of the resultant protein-detergent complex may be greater than that of solutions of either constituent alone.

Proteins of rod-like morphology (and both fibrinogen and gamma globulins conform to this description) have a greater viscosity than the globular proteins,

such as albumin. Houston and Lawrence (1955) have shown that both fibrinogen and gamma globulin are the protein fractions most likely to be increased in the plasma of tuberculous patients. The raised E.S.R. and the increased plasma viscosity are probably, therefore, both manifestations of the same factor, namely, the increased amounts present of these two protein fractions. The unfolding of the plasma protein molecules following the addition of detergent can be presumed from the increased viscosity, but this unfolding is paradoxically associated with a lowering of the E.S.R.

The nature of the change brought about by the detergent in the colloidal solution of the plasma proteins is not known. The progressive diminution of the E.S.R. with increase in the concentration of the detergent, the absence of the Du Nuoy phenomenon and the results of the electrophoresis of the serum-detergent mixture suggest that there is an immediate and complete reaction between the two components, of a simple chemical nature. It is significant that, without any alteration to the protein mass, but with change in the chemical and physico-chemical character of certain of the protein fractions, and of the colloidal solution as a whole, modification or even inhibition of the formation of the erythrocyte aggregate can be achieved.

Mass, therefore, is probably not the only factor to be considered in the evolution of a formula relating protein fractions to the E.S.R. One other factor to be considered, and one which Fahreus mentioned in his early work, is the influence of the electrical forces acting in the colloidal solution. Florey (1941) has shown that there is a marshalling of the protein molecules into a set pattern in colloidal solutions, and there is a hypothesis that this pattern derives from the electrical forces acting in the colloidal solution. The formation of aggregates from the negatively charged erythrocytes may be merely a reflection of this pattern of forces acting in the plasma. The cationic detergent, by reacting with the protein molecule, may cause a disintegration of this pattern, with consequent inhibition of aggregate formation.

Summary

Experiments are described which show that addition of small amounts of a cationic detergent to blood plasma causes a diminution in the erythrocyte sedimentation rate and an increase in the plasma viscosity. In the concentration used the detergent did not have any effect on the erythrocytes.

Electrophoresis of a similar serum-detergent mixture showed modification of the gamma-globulin and, to a lesser degree, in the alpha-2 and beta globulin peaks. Addition of calcium chloride solution to a plasma-detergent mixture failed to produce a fibrin clot.

There was a fall in the surface tension of the plasma-detergent mixture, but no Du Nuoy phenomenon was observed.

The significance of these findings is discussed, and the theory advanced that electrical forces acting in the colloidal solution of the plasma proteins have an effect on aggregate formation and, therefore, on sedimentation rate.

I wish to acknowledge my indebtedness to Dr. A. C. Penman and to Dr. J. S. Miller, Cheshire Joint Sanatorium, England, for helpful criticism and advice.

REFERENCES

ANSON, M. L., and EDSALL, J. T. (1948): " Advances in Protein Chemistry." New York.
CROOKE, E. M., HARRIS, H., HASSAN, F., and WARREN, F. (1954): *Biochem. J.*, **56,** 434.
FAHREUS, R. (1921): " Suspension Stability of the Blood." Stockholm.
FLOREY, J. (1941): *J. Amer. chem. Soc.*, **63,** 3083.
HAM, T. H., and CURTIS, F. C. (1938): *Medicine*, **17,** 447.
HARDWICKE, J., and SQUIRES, J. R. (1952): *J. clin. Sci.*, **61,** 333.
HARKNESS, W., HOUSTON, J., and WHITTINGTON, W. (1946): *Brit. med. J.*, **i,** 268.
HOUSTON, J., and LAWRENCE, J. S. (1955): *Brit. J. Tuberc. Dis. Chest*, **49,** 119.
JIRGENSONS, W., and STRAUMANIS, W. (1954): " Colloidal Chemistry." London.
MEYER, A. J., TREVORROW, V., WASHBURN, A. H., and MUGRAGE, E. R. (1953): *Blood*, **8,** 893.
PLUCKTHUN, H., and GOTTING, H. (1951): *Klin. Wochenschrift*, **15,** 6.
PUTNAM, F. W., and NEURATH, J. (1945): *J. biol. Chem.*, **159,** 195.
ROURKE, M. D., and ERNSTENE, A. C. (1930): *J. clin. Invest.*, **8,** 545.
SCHUTT, E. D. (1928): *Svenshia Lü*, **25,** 1009.
STEELE, F. (1948): *Bull. Inst. med. Lab. Tech.*, **14,** 78.
SYKES, W. (1948): *Brit. med. Jour.*, **ii,** 393.
T'ANG and WANG (1941): *J. trop. Med. Hyg.*, **44,** 5, 28.

Brit. J. Dis. Chest (1959) **53**, 75.

LARYNGEAL TUBERCULOSIS*

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General Considerations

The modern era of treatment in pulmonary and extra-pulmonary tuberculosis is now of about ten years' duration. During this period the many excellent contributions to the literature have not only accentuated the rapid therapeutic progress but also the relative futility of previous measures. Just how much the patient did for himself, prior to ten years ago, and how much the physician did for him will always be a moot question. The excellent overall results which have been accumulating during the past decade have been so thoroughly stressed and documented that they have been universally accepted as basic and unequivocal. The drugs which have been responsible for this fact have carried with them certain side-effects and have, in some cases, dampened the results.

There are some who consider streptomycin (or its derivative, dihydrostreptomycin) as the main attack on laryngeal tuberculosis. This, of course, is not true. Then, too, optimum dosages have not yet been resolved. The protean manifestations of the disease, as well as individual patient response, preclude for the moment its close standardisation. Until now the reaction of the patient as well as the extent and duration of the disease have been the source of definite, even though mild, confusion.

Since in laryngeal tuberculosis we are always considering a complication of severe pulmonary tuberculosis it is of the utmost importance that the primary disease also benefits from the therapy. The laryngologist and the physician must, therefore, co-operate in each case where these two conditions co-exist. Usually pulmonary and laryngeal tuberculosis will respond in a like manner, up to a certain point. Many cases are on record whose laryngeal response was rapid and lasting but whose pulmonary condition became either stationary or worse, whereas the pulmonary disease should receive therapeutic priority.

As a general rule, antibiotics produce the best results in direct proportion to the acuity of the disease. Beyond a certain point of chronicity the value of these substances becomes limited, not only in tuberculosis, but in other bacterial infections as well. This seems to be associated with developing fibrosis and its relatively poor blood supply. Relative or complete resistance may also develop, but this is not too great a problem with the antituberculosis drugs at the present time. Fibrotic laryngeal tuberculosis accounts for practically all of our very occasional poor or delayed results.

* Compiled from all available tuberculosis hospital beds in the county, this survey covers virtually all cases of laryngeal tuberculosis found since 1940. This county contains about 1 per cent. of the population of the United States and so for statistical purposes is considered representative of the entire national population.

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The laryngeal disease will usually mirror the type found in the lung. This may be fibrotic, exudative or mixed, with one of the first two usually dominant. Prior to modern therapy exudative laryngeal and/or pulmonary tuberculosis were the most difficult to treat, the former hardly responding at all to existing methods. With modern therapy the prognosis is far better in exudative disease, laryngeal or pulmonary, than in fibrotic, even though at the onset it is usually more distressing. Though fibrotic laryngeal disease is frequently met with in our three local sanatoria, we have found that this type of disease responds much better than its equivalent in the lung. This might be explained by the blood supply being more abundant in the larynx than in the pulmonary tissue. It is also a different type of tissue and may sustain more local immunity. Another factor might be that most of the pathology in the larynx is that of macroscopically and microscopically draining abscesses. It has been observed for some time that the antituberculosis drugs act far better in draining lesions and those confined to the canalicular systems of the body (*i.e.* the air passages, the genito-urinary and gastro-intestinal systems) than they do in the solid or semi-solid organs. All other sites have a high potential for excisional surgery.

Diagnosis

Tuberculosis of the larynx is never primary; there are no well-documented cases to the contrary. The laryngologist who is confronted with hoarseness should first obtain a history relative to the chest, which may be vague if the pulmonary disease is fibrotic. Many patients believe that their disease started with a cold, influenza or grippe. Since these follow a fairly characteristic course any deviation is suspect. Because tuberculosis of the larnyx is always secondary, the laryngologist has a very important clue available. Once the first flush of early tuberculosis has subsided, and unless it becomes secondarily infected or trapped, it usually resolves itself into an essentially silent disease from the subjective viewpoint. It is felt by many that any pain accompanying laryngeal tuberculosis is due to secondary infection. Should the patient consult the laryngologist for hoarseness, with or without pain, and advanced pulmonary tuberculosis is subsequently established, specific laryngitis is by far the most likely diagnosis.

Other than being constant, the type of hoarseness is not characteristic. An appreciable number of hoarseness cases seen in our in-patient clinics are due to some sort of compromise of the recurrent laryngeal nerve system. This causes a lowered register, in contrast to the harsh dysphonia noted in proliferative or destructive disease; it is more pronounced later in the day and is usually intermittent. The recurrent laryngeal nerve may be adversely influenced by mediastinal shift and adjacent pleurisy in pulmonary tuberculosis. Enlarged mediastinal glands and tracheo-bronchial shift may also be the cause of stress or strain on these nerves. The patient may have a dysphonia due to a local manifestation of generalised myasthenia. These aetiologies are much more common in our clinics than those due to specific cord involvement.

Pain has never been a constant criterion in laryngeal tuberculosis, except in epiglottal involvement, and its absence should not be misleading. Under proper treatment the pain is cleared rapidly, although epiglottal ulceration may

be most stubborn and persistent, since the epiglottal pathology involves the chondrium as well as the perichondrium. Should pain be present it may be so severe that fluids and food may be refused by the patient. If such a patient be neglected he may not only be in the throes of severe pulmonary tuberculosis but rapidly advancing dehydration and malnutrition as well. Should a patient have other conditions as well, dire results will always follow unless proper therapy is instituted at once.

Once laryngeal tuberculosis is suspected the very first diagnostic consideration should be a chest film. Auscultation, percussion or even a temperature recording may not suffice even in moderately advanced cases. Should râles be present they may sometimes be heard quite well through the open mouth. In this community almost everyone has had one or more chest films and is informed of the results. Sputum examination may be intermittently negative even with cavitation, particularly in fibrotic disease. After a patient has been on antituberculosis therapy a positive sputum or culture may be found only after repeated tests, and these may take as long as six weeks, for under therapy the organisms are too weak to grow or may not be present in the material submitted. It appears that modern therapy quickly knocks out those bacilli which are free-floating, while those locked in fibrotic foci become elusive.

The appearance of the larynx is that of destructive disease; in contrast, neoplasm represents proliferation. Unless secondary infection has supervened there is very little reaction about the ulceration and only careful and repeated inspection will indicate the diagnosis. Any attempt to differentiate malignant and specific infectious lesions of the larynx by their location may mislead the laryngologist into the unlikely realm of statistical diagnosis. Localised lesions may occur anywhere in the larynx, or there may be total involvement, superficial or deep. My experience has been that the cords are most frequently involved at the onset and that the lesion is more apt to spread to other parts of the larynx by continuity. Since the cords are covered by stratified squamous epithelium they are unprotected by ciliary activity and are probably more susceptible to implantation of the tubercle bacilli.

Owing to the trauma of coughing and the early membranal response to tuberculoprotein, the larynx may show intense injection and œdema at the onset of pulmonary tuberculosis. These two factors may produce hoarseness, but not pain; this picture is not to be confused with laryngeal tuberculosis *per se*.

For some unexplained reason tuberculosis of the larynx tends to remain within the confines of this organ and almost never spreads to the hypopharynx or the subglottic regions. This is not generally true of a malignancy or non-tuberculous lesion in this area. In malignancies and non-tuberculous lesions we not infrequently see regional lymph node manifestations in the cervical chain. I have no record of ever having seen proven cervical tuberculous adenitis secondary to laryngeal involvement.

An immediate biopsy of undiagnosed laryngeal lesions is always a temptation, but the limitations of making a definite diagnosis with superficial biopsy material from the larynx are well known and deep biopsy of the larynx from an already destructive lesion may well cause irreversible physiological damage.

In view of the rapid and excellent results with modern therapy it would seem that the patient deserves a therapeutic trial, with biopsy as a later aid if needed.

Should pain be a prominent feature it is almost certain that this symptom can be practically eliminated within a week or less, under proper therapy. This was an unexpected finding and even to-day is not easily explained. Secondary infection may well play an important role. On the other hand, the antituberculosis drugs have a limited spectrum and would not be expected to react favourably in any secondary laryngeal infection. Even though the pain has subsided in a few days the appearance of the larynx will not have changed within two or three weeks. Because of this fact and the cessation of pain, if present, we have available two important diagnostic criteria. Should the pain fail to recede rapidly or the appearance of the larynx show little improvement, the relatively short delay will be of little importance if some other diagnosis becomes a possibility, whereas by the time a satisfactory biopsy or culture has been obtained valuable therapeutic time may have been lost.

Incidence

Even a cursory review of the literature on laryngeal tuberculosis discloses a startling disparity among different authors on the incidence of this complication. Some contributors have claimed that about one-third were afflicted prior to the use of the specific antimicrobials. Others have felt that about 5 per cent. should have been the figure. My own feeling is that it should have been even less than this. It seems to me that the higher figures were wrong for several reasons; tuberculinisation, irritating secretions and trauma due to coughing. Any of these would produce hoarseness, and if this symptom is used as the most important criterion in diagnosis, the incidence pattern will be unreliable. Many cases of hoarseness would recover within a week or ten days without any therapy beyond supportive measures. Tuberculosis is always chronic and, unless specific measures are employed, rapid resolution of pulmonary or extrapulmonary tuberculosis is not the rule.

The true incidence of laryngeal tuberculosis cannot yet be accurately stated. Table 1 shows the number of cases seen in comparable periods, before and after antituberculosis drugs, from 1940 through 1954. Many of those in the later period were holdovers from the previous one. It is noteworthy that the total number fell dramatically after the drugs were introduced. Certainly there are fewer cases today because patients who are under adequate pulmonary therapy do not develop laryngeal tuberculosis, once the pulmonary disease has been brought under control, unless the case is terminal or about to become so. It must also be assumed that an appreciable number of patients have incipient lesions whose early therapy has prevented them from reaching the clinical horizon. Patients with pulmonary tuberculosis are generally placed under therapeutic protection without delay so that the time interval between starting therapy and their laryngeal examination in the hospital may be such that very early and mild cases become clinically impossible to detect. A community such as this, which is constantly surveying its members, particularly those living in

areas where tuberculosis is more prevalent, has reduced the number of cases which, if left undetected, would certainly become advanced and thus be more likely to develop laryngeal tuberculosis.

It is felt that those having a true positive tuberculin test have within themselves a nidus of live tubercle bacilli (which, when dead, produce the endotoxin known as tuberculin). To-day figures are not generally available showing the number of people who have a positive tuberculin reaction, but the number of tuberculosis deaths in this county are known (Table 1) and are included in this paper to demonstrate the results of modern procedures.

TABLE 1.—INCIDENCE AND MORTALITY OF LARYNGEAL TUBERCULOSIS IN CUYAHOGA COUNTY

Year	*Laryngeal tuberculosis*									*Deaths † all TBc*
	County Hospital		*City Hospital*		*VA Hospital*		*Total*			
	Cases	*Deaths*	*Cases*	*Deaths*	*Cases*	*Deaths*	*Cases*	*Deaths**	*Per cent. Deaths*	
1940 ..	8	2	71	35	—	—	79	37	47	—
1941 ..	6	0	44	25	—	—	50	25	50	579
1942 ..	8	3	55	28	—	—	63	31	50	564
1943 ..	8	2	58	47	—	—	66	49	74	582
1944 ..	5	3	39	28	—	—	44	31	70	552
1945 ..	8	7	35	29	—	—	43	36	84	536
1946 ..	3	3	44	39	—	—	47	42	89	527
				Antimicrobial		*era*	*begins*			
1947 ..	2	1	29	28	—	—	31	29	94	534
1948 ..	2	1	14	7	16	8	32	16	50	484
1949 ..	10	6	28	20	16	5	56	31	55	404
1950 ..	4	0	21	9	11	2	36	11	31	305
1951 ..	6	2	10	4	15	2	31	8	20	264
1952 ..	9	2	7	2	5	1	21	5	24	235
1953 ..	4	0	6	1	6	1	16	2	13	205
1954 ..	4	1	5	1	5	0	14	1	7	178

* *Signed out dead.* † *County health figures.*

The recent registered cases and case findings for the county are as follows:

	Registered cases of tuberculosis	*New case findings of tuberculosis*
1949	9,722	4,851 (mass survey)
1950	12,626	1,896
1951	14,006	2,165
1952	13,013	2,236
1953	12,756	1,804
1954	11,770	1,777
1955	10,352	1,437

There has been no dramatic annual fall in the positive findings in recent years and these figures are included because each one of these, if left undiscovered or neglected, is a potential case of laryngeal tuberculosis. Should

the present vigilance be relaxed we could expect that all types of tuberculosis would again become a major problem.

Treatment

The tubercle bacillus has been empirically and specifically under a state of siege for many centuries. Its metabolism and chemical composition have been the subject of intense and constant research for decades. These investigations prior to the introduction of streptomycin appear now to have been of scientific interest only.

Initially costly and scarce, streptomycin, isonicotinic acid hydrazid (INAH) and para-aminosalicylic acid (PAS) are to-day the most widely used drugs in pulmonary and extra-pulmonary tuberculosis.

Streptomycin: For the first years after its introduction, the dosage was 1 to 3 g. daily for an indefinite period. This period was usually determined either by the development of resistant organisms or toxic symptoms, or both. The drug was later given with PAS, whose dosage is about 12 g. daily. Because of its somewhat alarming toxicity on the vestibular portion of the eighth nerve. dihydrostreptomycin was developed as a substitute, but has now largely been discarded in our three sanatoria on account of the delayed, unpredictable and irreversible damage to the acoustic portion of the eighth nerve when given in large dosages. Having had the opportunity of comparing the effects on the larynx of these two substances, it became evident that the analogue did not act as rapidly or as well as the parent substance. The purification and regulation of streptomycin has also contributed to the relative disuse of dihydrostreptomycin, which is not now in general use in this community.

INAH: After the wild enthusiasm of its début in 1950 had subsided, this substance gradually emerged as therapeutically equal in importance to its predecessor, streptomycin. Substantial evidence has been accumulating that it is even somewhat superior. It is now given in a daily dosage of about 300 mg. with PAS, usually 12 g. daily, and has the advantage of being given orally. Streptomycin, on the other hand, is absorbed hardly at all by the intestinal tract and must be given by injection. INAH was at one time given in a dosage of about 600 mg. daily; but owing to its toxic manifestations the dosage has been reduced to about half that amount.

PAS: This material came into general use several years after the introduction of streptomycin. It was thought at first that it had strong anti-tuberculosis properties, but it is now known that it has practically none when given alone. Its value to-day is that, when given in conjunction with streptomycin or INAH, the development of resistant organisms is either delayed or prevented. Whatever the regimen it is usually given in a daily dose of about 12 g. in adults.

These three medicaments may be given in different combinations. If streptomycin-PAS is considered the combination of choice, and the laryngeal tuberculosis is deemed severe, 1 g. of streptomycin with 12 g. of PAS are given daily for a week or ten days. The protocol is then changed to 1 g. of streptomycin twice-weekly and 12 g. of PAS daily. This is the pulmonary schedule, but is suitable for the laryngeal as well. When streptomycin-PAS was given

daily over a longer period of time the larynx responded more rapidly, but to-day the results, although slightly delayed, are the same. The twice-weekly streptomycin regimen has now been given to numerous patients for a period of about five years with very few showing resistant organisms or important toxic symptoms.

If all three of these drugs are given simultaneously, careful regulation must be observed or the patient may not only be in dangerous therapeutic territory but may also be running the risk of wearing out his medications. We believe that the laryngeal therapy should be rationed as closely as possible so that the patient may be eligible for a long-term pulmonary schedule. This precaution is observed also because the surgeons may want the patient therapeutically insured if surgery is a future possibility. To a large extent, modern thoracic surgery in pulmonary tuberculosis owes its low morbidity and mortality to-day to proper medical management.

The selected schedule must, of course, be elastic and only experience will dictate the optimum one for the patient. The short time that it takes to bring the larynx under control presents few problems to the physician relative to pulmonary regulation.

Should the above schedules fail to produce satisfactory results, or the patient, for one reason or another, be unable to tolerate them, other medications may be tried. Among these are Tibione, Viomycin, Cycloserine and Pyrizinamide. Others are being tried but are not past the experimental stage and should not be administered except under careful supervision in the last resort.

Streptomycin-PAS-INAH combinations have recently been recommended by a governmental agency and a daily streptomycin dose of 1 g. prescribed. This increased dosage of streptomycin is causing some concern, particularly since it is planned to carry on this routine for a period of eight months.

Caloric and audimetric tests are being done on these patients at the onset of therapy and every two or three weeks thereafter, but since this régime has only been in force for about eight months statistics are not yet conclusive.

Prior to the forms of therapy described we had little to offer the patient with laryngeal tuberculosis other than vocal rest, actual cautery and supportive measures. It seemed then that some of the milder cases were self-limited and did well with no more than symptomatic therapy. Certain medicinals caught the passing fancy from time to time, but their inevitable inefficiency allowed them to pass into medical history. We do not advocate voice rest at the present time because we feel that a modest amount of movement of the vocal cords seems conducive to a better voice following the healing period. Nor have we found it necessary to resort to cautery since the introduction of streptomycin.

Toxicity of Modern Therapy

The three principal medicaments employed in tuberculosis have certain side-effects in common: dermatoses, liver and kidney damage, gastro-intestinal disturbances, blood dyscrasia, "drug-fever," sensitivity and allergy. Besides these, each one may have one or more characteristic undesirable actions:

STREPTOMYCIN:	Vestibular dysfunction
	Ocular disturbance
	Slight impairment of hearing
	Paresthesias
	Grogginess
INAH:	Hyperreflexia
	Peripheral neuritis
	Cochlear damage
	Vestibular dysfunction (rare)
PAS:	Tinnitus
	Gastric irritation

Vestibular and cochlear tests were made in two sanatoria with daily streptomycin or dihydrostreptomycin in about 200 cases. The results were:

STREPTOMYCIN	DIHYDROSTREPTOMYCIN
Hearing	*Hearing*
Impaired .. 12%	Impaired .. 16%
Improved .. 18%	Improved .. 21%
Dizziness	*Dizziness*
20%	4%

It is generally believed that dihydrostreptomycin has a predilection for the cochlear branch of the eighth nerve and that streptomycin is more toxic to the vestibular component. We found in doing audiometric studies that there is not much difference between the two in relation to hearing impairment. As may be noted, there might be a definite and comparable improvement in hearing. The impairment (and improvement) was at the edge of and beyond the conversational range, being more than 5 decibels but seldom more than 20. The patients, therefore, had few if any complaints relative to hearing acuity unless they had had a previous deficiency. We are unable to account for the mild improvement shown by some patients other than to postulate that tuberculin is neurotoxic to the acoustic portion of the eighth nerve.

In caloric tests we have never been able to correlate the degree of nystagmus with the degree of dizziness.

These tests were all carried out by the author under constant conditions. Meningeal and miliary tuberculosis were at one time almost universally fatal and large dosages over a long period of time are felt to be justifiable. Under such a schedule total loss of hearing with dihydrostreptomycin and total loss of vestibular function with streptomycin have been observed. These facts are included inasmuch as there is now a tendency toward an increase in dosages.

Mild eighth nerve symptoms with twice-weekly streptomycin may emerge in a definite pattern on the days the medication is given. These may come on within an hour and last for twenty-four hours. We cannot account for these other than that they are neurological in origin. The findings are: 1. Inability to focus well; 2. Perioral paresthesia; 3. Mild disturbance of equilibrium; 4. Mental dullness. These symptoms appear in an appreciable number of patients and may concern not only the otolaryngologist but also the ophthalmologist. Since they are transitory we feel no marked concern at the moment, but we must be aware of possible cumulative effects.

Dosage regulation, drug purification and the production of various accept-

able salts of the anti-tuberculosis medicaments have reduced toxicity to a relatively minor status to-day, but its emergence must be considered as an ever-present threat to optimum results.

General Outlook

Whatever the complications occuring in pulmonary tuberculosis, it is most important to concentrate on the primary disease. Patients to-day may not necessarily be very ill when their laryngeal disease is discovered and the most important symptom of hoarseness may be of small concern to them. If tuberculosis of the larynx is diagnosed we tell them at once and at the same time explain that their laryngeal outlook is indeed excellent. As soon as the larynx has shown definite improvement the patient may be lulled into a false sense of security and assume that his pulmonary pathology has shown as rapid and as excellent results as his larynx, but because the pulmonary disease is advanced and the pulmonary response not nearly as good as that of the larynx, his ultimate prognosis is not as good as he thinks. This should be communicated to the patient, who should be encouraged to follow the course of treatment recommended by the laryngologist.

Case History

White. Female. Married. Age 22, 9.12.47.

Diagnosis: Far advanced exudative pulmonary tuberculosis; endobronchial tuberculosis with tension cavity; extensive exudation laryngeal tuberculosis; pregnancy 6-7 months. The patient had severe dysphagia and was able to take only a limited amount of fluids and food. Under streptomycin the pain cleared in five days and a return of normal voice was noted 1.6.48. Streptomycin was given in a dosage of 1 g. daily from 13.12.47 to 15.1.48. This was then dropped to ½g. daily to 25.2.48. She was delivered of a normal child 13.2.48. Baby and mother were discharged with medical approval 27.2.48; at that time sputum and gastric washings were negative. The larynx appeared normal.

This represented our first pregnancy case treated with streptomycin, and a slight delay is noted before therapy was started because of the possibility of unpredictable eighth nerve damage on the fœtus. Cord and maternal blood streptomycin levels were obtained at the time of delivery. These were the same: 0·6 microgram per millilitre. The child has never shown any evidence of vestibular or cochlear damage. Subsequent cases of pulmonary tuberculosis in pregnancies, with or without complications, have shown no eighth nerve difficulties in the child.

Before the advent of antituberculosis drugs one could only say that the lesions of laryngeal tuberculosis were under control or quiescent, but to-day, after twenty years' experience, we are able to state a recurrence is unlikely if the patient adheres to the regimen prescribed. Even excluding terminal recurrences the total number of recurrences is a small fraction of 1 per cent.

While under optimum treatment for pulmonary tuberculosis the possibility of the patient developing laryngeal tuberculosis is practically nil. Should this unfortunate situation occur the prognosis is hopeless, not because of ineptness

of the drugs but because he has lost, or does not have, the ability to convert them into therapeutic substances.

Many cases of hoarseness are noted in patients who have been discharged from the Ear-Nose-Throat departments. These may or may not have had tuberculosis of the larynx, but are usually due to a non-specific laryngitis or a compromise of the recurrent laryngeal nerve system. The latter will usually manifest itself by a paresis of one vocal cord, a condition seen frequently, and is usually *not* accompanied by hoarseness if this be of gradual onset.

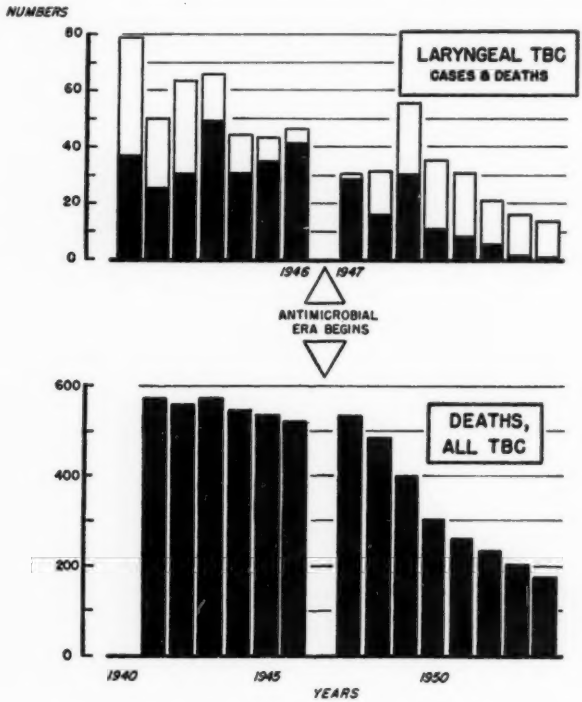

FIG. 1.—Laryngeal tuberculosis cases and deaths

The bar-graph (Fig. 1) shows that patients with laryngeal tuberculosis are in a more unfavourable category than those with uncomplicated disease, because the pathology has become extra-pulmonary and tuberculous manifestations are likely to exist. Since these may be silent they may be found only at autopsy, but contribute to the patient's general deterioration.

The compiled figures are from the County, City and Veterans Hospitals for tuberculosis. They represent like periods which occurred before and after the introduction of specific anti-tuberculosis drugs.

The County unit for tuberculosis has been followed since 1936, the City

Hospital unit since 1945 and the Veterans Hospital since 1947. During this time one otolaryngologist (the author) followed all cases of tuberculosis of the larynx which were admitted to each unit.

The principles of diagnosis and treatment are outlined and also the incidence and general outlook of laryngeal tuberculosis relative to the primary disease.

The spectacular decline in mortality has not been proportionate to the morbidity in tuberculosis. The tuberculous population in this area has been nearly constant through new case findings and, to a lesser degree, relapses. Each new case finding, each positive tuberculin, each registered case and each relapse is a potential case of laryngeal tuberculosis.

Summary

General considerations are presented concerning the complication of laryngeal tuberculosis. It is never primary and occurs in advanced pulmonary tuberculosis.

The diagnosis is made by inspection and the therapeutic trial of the three current drugs in use: streptomycin, isonicotinic acid hydrazid and para-aminosalicylic acid. Biopsy is not in use unless other disease is concurrently in evidence. The side effects are pointed out and are considered to be a minor therapeutic risk; the hazards of therapy are documented.

Figures are presented to stress that while the results of treatment in laryngeal tuberculosis are indeed excellent the patient is not as well off as he thinks he is because he has advanced pulmonary tuberculosis. This does not respond as well as does the larynx; modern therapy is much more satisfactory in the hollow, or canalicular, portions of the body than in solid or semi-solid organs.

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THE DIAGNOSIS OF TUBERCULOUS PLEURAL EFFUSION*

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"Pleurisy, in some one or other of its forms, has in all ages attracted the marked attention of practitioners: on this account its literature is extremely extensive."—John Forbes, 1829.

Introduction

Until recently no satisfactory method existed for proving the diagnosis in the majority of patients with a presumed primary tuberculous pleural effusion (see Tables II, III, IV, V, VI). Now pleural biopsy gives a positive diagnosis in about 80 per cent. of these patients (Mestitz *et al.*, 1958). Using this as a yardstick we have analysed a number of indirect aids in the diagnosis of tuberculous effusions in an attempt to ascertain which if any of these are of clinical value. Below we consider 112 cases of pleural effusion of proven ætiology (see Table VI) in whom the elucidation of the cause of the effusion had been the foremost clinical problem—*i.e.* Group I cases (Mestitz *et al.*, 1958).

Table I.—The Symptoms on Admission of Patients who were given a Definite Final Diagnosis

Symptom	*Final diagnosis*		
	T.B. 73 *cases*	*Malignant* 30 *cases*	*Pyogenic* 9 *cases*
Pain in chest ..	68	23	7
Cough	39	15	4
Dyspnœa	30	16	4
Lassitude	23	4	1
Weight loss	9	10	1
Anorexia	8	2	1
Sputum	8	6	3
Hæmoptysis ..	7	7	2
Sweats	7	1	—
Eryth. nod.	3	—	—
Symptom free ..	1	—	—

* This paper is based on work submitted for the degree of M.D. in the University of London by one of us (P.M.).

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Clinical Presentation

No single symptom has any decisive value in differential diagnosis (Table I). An analysis of symptoms in a series of patients with presumed tuberculous effusions is given by Züst (1946), Karron and Purves (1947), Kraft (1949), and Skaggs and Smiley (1955). Chest pain is the commonest complaint, but the relative frequency of other symptoms varies considerably. For instance, Grant (1952) says, ". . . cough is rarely present in primary tuberculous effusions unless manifest pulmonary tuberculosis coexists," yet Young and Beaumont (1950) consider cough to be a very common symptom.

We share the generally accepted view that an insidious onset favours a tuberculous ætiology, particularly in the young, while an explosive onset suggests a pyogenic cause. This rule of thumb is wrong sufficiently often to be of limited value and several of our cases have indeed been exceptions to this rule. Other authors have found the same exception (Dunin, 1887; Korns, 1926; Gsell, 1930; Farber, 1943; Feldman and Lewis, 1946; Kraft, 1949; Robson, 1952; Barnwell, 1955). In our series it was extremely rare, whatever the speed of onset of symptoms, for a tuberculous effusion to make its first appearance after the patient had been seen in hospital; the effusion, if tuberculous, was nearly always present when the patient was first seen. Conversely, if a patient becomes sufficiently sick to go to hospital before fluid has formed, he probably has an underlying pneumonia (Robson, 1952).

Fever was present on admission in 60 out of 73 proved tuberculous effusions, in 11 out of 30 malignant effusions, and in all the pyogenic effusions. Many authors have also found fever to be common at the onset of tuberculous effusions; yet Forgacs (1957) found it in only 41 out of 169 presumed tuberculous effusions.

The age of patients with tuberculous effusions ranged from 17 to 51 years. Robertson (1952) has pointed out that 10 per cent. of all primary tuberculous effusions occur in people over the age of 40.

The size of the effusion was of no help in the differential diagnosis.

The Tuberculin Skin Test

This was carried out in 66 of the 73 patients with a proven tuberculous effusion and was positive in every one of them. Since the tests were not done in a standardised manner, no attempt has been made to analyse the degree of skin sensitivity shown by these patients.

We have not encountered any cases of proved tuberculous effusion with a negative skin tuberculin test, nor have we been able to obtain details of such a case from any of our colleagues. Thus we consider a negative 1/100 Mantoux test to be very strong evidence indeed against a pleural effusion being tuberculous. Pagel *et al.* (1953) and Roper and Waring (1955) are in agreement with this view. Other authors such as Farber (1943) and Feldman and Lewis (1946) include a few patients with a negative tuberculin test in their series of tuberculous effusions, but the diagnoses in these cases were based on the clinical picture and were not substantiated.

Laboratory Investigations

The erythrocyte sedimentation rate was recorded in 72 of the 73 tuberculous cases, and in 27 of the 30 malignant cases. Taking both groups together the values vary between 11 and 118 mm./hr. (Westergren), except in two cases of malignant disease in whom it was 2 and 5 mm./hr. (Fig. 1).

Roper and Waring (1955) showed that the E.S.R. is of no value in the initial investigation of a pleural effusion. Our own results suggest that the E.S.R. is of no value in the differential diagnosis between malignant and tuberculous effusions.

The fluid in primary tuberculous pleural effusion is usually clear amber or greenish-yellow; but it may be turbid, or frankly blood-stained (Paddock, 1940; Vaizey and Perry, 1940; Berliner, 1941; Tinney and Olsen, 1945). In one of our 73 proven cases of tuberculosis the fluid was bloody; in none was it frankly purulent.

The pleural fluid cytology was examined in 68 of the 73 patients who were proved to have a tuberculous effusion.

(*a*) In one the fluid was reported as being " almost pure blood."
(*b*) In one the cells were " mainly endothelial cells."
(*c*) In one, the differential count was " 50 per cent. polymorphs, 50 per cent. lymphocytes."
(*d*) In 65 out of 68, lymphocytes predominated, and where a formal differential count was done, the percentage of lymphocytes was always more than 72 per cent., and more than 85 per cent. in the great majority.

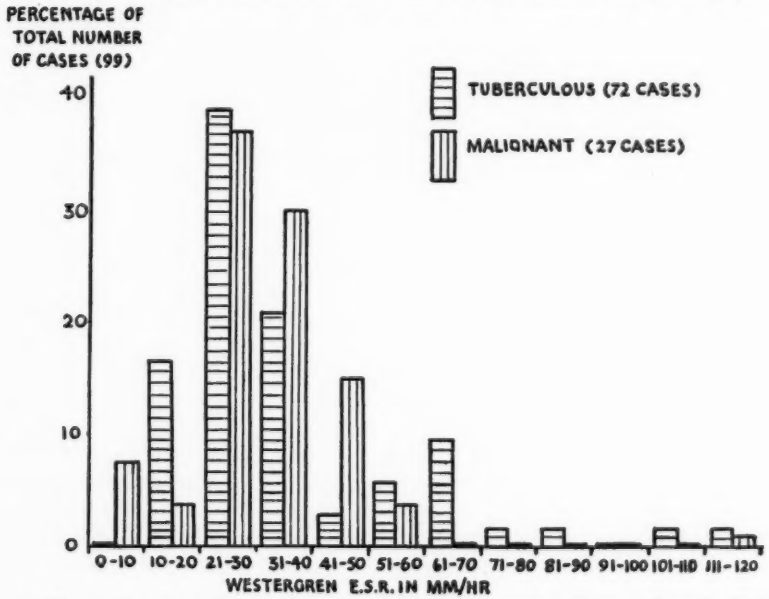

Fig. 1. The erythrocyte sedimentation rate in tuberculous and malignant pleural effusions.

(*e*) In only one of our proved cases of tuberculous pleural effusion did polymorphs predominate in the fluid.

We saw two cases which on clinical grounds were presumed to have a tuberculous effusion in spite of a very high polymorph count in their fluid; one turned out to have a non-tuberculous (post-pneumonic) effusion, the other a carcinoma of the lung.

Our conclusions on the value of pleural fluid cell counts are as follows:

(*a*) In a pleural effusion of recent onset, where no antimicrobial therapy has been used, a lymphocyte count of 70 per cent. or more in the fluid is compatible with a tuberculous basis to the effusion.

(*b*) A differential fluid cell count which shows more than 50 per cent. polymorphs is a pointer against tuberculosis, though it does not disprove it. Persistence of a high polymorph count, and in particular, failure to isolate tubercle bacilli from such fluid, is very strong evidence against the effusion being tuberculous.

(*c*) All other interpretations of pleural fluid cytology, with the exception of the finding of malignant cells, and L.E. cells, are of very doubtful validity.

Since the work of Widal and Ravaut (1900) a large literature has appeared on this subject (see Königer, 1908; Spriggs, 1957). Rarely high polymorph counts may be found in tuberculous effusions (Korns, 1926; Frederiksen, 1934; Maclean, 1948; Emersen, 1957). The significance of this is controversial, but several reports suggest that tubercle bacilli can very often be recovered from such fluids (Foord *et al.*, 1929; Kraft, 1949).

The Recovery of Tubercle Bacilli from Pleural Fluid

Direct examination of serous pleural fluid smears for tubercle bacilli is seldom helpful. Literature reports are very scanty: Pinner and Moerke (1930)

Table II.—The Results of Culture of the Pleural Fluid in Patients with Presumed Tuberculous Effusions (*i.e.*, not including Guinea-pig Inoculation)

Authors	*No. of Patients (from whom fluid was cultured)*	*No. of positive cultures*	
Tomita, 1939	347	248	(71·8%)
Carstensen, 1940	57	41	(71·9%)
Karron and Purves, 1947	50	10	(20·0%)
Thompson, 1947*	23	5	(21·2%)
Eberle, 1949	14	14	(100%)
Kraft, 1949*	30	2	(6·7%)
Ives and McCormick, 1956	95	86	(88·5%)
Emerson, 1957*	100	17	(17·0%)

* None of the patients in these series had visible parenchymal disease at any time during their stay in hospital.

found tubercle bacilli on direct smear in 3 out of 32 pleural fluids, but all their patients had frank pulmonary tuberculosis. Karron and Purves (1947) found direct examination positive in 6 out of 71 fluids from patients with " tuberculous pleurisy with effusion," but 42 per cent. of their patients had parenchymal disease, and an unspecified number of fluids were in fact purulent. Wynn-Williams and Shaw (1955) failed to find tubercle bacilli on smear in any of their 102 fluids. We found that of the 40 cases of tuberculous effusion which were recorded as having had one or more pleural fluid deposits examined directly for tubercle bacilli one only was positive, and this was subsequently confirmed both by pleural biopsy and guinea-pig inoculation; the fluid contained 90 per cent. lymphocytes.

The results of culture and guinea-pig inoculation of the fluid from patients with presumed primary tuberculous effusion vary enormously (see Tables II and III). Close (1946) has shown how meticulous attention to details of laboratory technique can improve the results of culture on Lowenstein-Jensen medium, and other media and methods have been claimed to yield better results. (See in particular Magath and Feldman, 1932; Oshima *et al.*, 1933; Eberle, 1949; Willis and Cummings, 1952; Ives and McCormick, 1956.) Falk (1950), discussing idiopathic pleural effusions, thought that *routine* culture and guinea-pig inoculation could be expected to be positive in 20 to 35 per cent. of large numbers of cases. In Table IV we have listed a number of reports to show the range of success in isolating tubercle bacilli, using one or more methods, from

TABLE III.—THE RESULTS OF GUINEA-PIG INOCULATION OF THE PLEURAL FLUID IN PATIENTS WITH PRESUMED TUBERCULOUS EFFUSIONS

Authors	*No. of Patients (from whom fluid was inoculated)*	*No. of Positive Guinea-pig Inoculations*	
Chauffard and Gombault, 1884	20	10	(50·0%)
Le Damany, 1897	54	47	(87·4%)
Japhé, 1913	26	8	(30·8%)
Silberschmidt (1924-25)	1,043	518	(50·0%)
Korns, 1926	53	19	(35·8%)
Gaarde, 1930	79	22	(27·8%)
Arborelius, 1930	112	72	(64·3%)
Gsell, 1930	94	52	(55·3%)
Carstensen, 1940	54	15	(27·8%)
Bonilla, 1942	34	14	(41·2%)
Farber, 1943	66	19	(28·8%)
Karron and Purves, 1947	32	17	(53·1%)
Kraft, 1949	51	18	(35·3%)

the fluid of patients with presumed tuberculous effusions. We have included our own results in Table IV and it will be seen that in 84 patients who had an " idiopathic " pleural effusion, tubercle bacilli were found in the fluid by culture and/or guinea-pig inoculation twenty-four times. We have not found any striking difference in results as between culture and animal inoculation.

TABLE IV.—A SELECTION OF PUBLISHED REPORTS TO SHOW THE RANGE OF SUCCESS CLAIMED FOR THE RECOVERY OF TUBERCLE BACILLI BY ALL METHODS FROM THE FLUID OF PATIENTS WITH PRESUMED TUBERCULOUS PLEURAL EFFUSIONS

Authors	*Number of cases of idiopathic effusion in whom fluid was examined*	*Fluid positive on culture and/or G.P.I.*	
Mumme, 1939	59	24	(51·2%)
Feldman and Lewis, 1946	21	5	(23·8%)
Emerson, 1954	40	6	(15·0%)
Roper and Waring, 1955	99	51	(51·5%)
Myers, 1955	192	76	(39·6%)
Skaggs and Smiley, 1955	29	7	(24·1%)
Wynn-Williams and Shaw, 1955	91	19	(20·9%)
Falk and Stead, 1956	591 cases. ? number of fluids examined	?	"20·0%"
Mestitz, Purves and Pollard, 1958	84*	24	(28·6%)

* Of these 84 cases, 73 were proved to have a tuberculous effusion.

Only in the series of Emerson, Roper and Waring and our series is it certain that patients with frank parenchymal disease or tuberculous empyema were excluded.

OTHER TESTS ON PLEURAL FLUIDS

Foord *et al.* (1929), Pinner and Moerke (1930), and Zinneman *et al.* (1957) report on various chemical tests on pleural fluids. Pinner and Moerke, Nassau (1941), Gelenger and Wiggers (1949), Calnan *et al.* (1951), and Engeset and Lygren (1953) have used the pleural fluid glucose content as an aid in diagnosis. Falk (1950) did not consider any chemical laboratory tests of much use. We have no information to offer on the value of such tests.

TABLE V.—THE NUMBERS OF DEFINITE DIAGNOSES MADE IN FOUR LARGE SERIES OF PLEURAL EFFUSIONS. (SEE ALSO TABLE VII, MESTITZ *et al.*, 1958)

Authors	*Total cases*	*Definite diagnosis*				*No definite diagnosis*
		T.B.	*Malignant*	*Others*	*Total*	
Vaizey and Perry, 1940	308	70 (22·7%)	91 (29·5%)		161 (52·3%)	147 (47·7%)
Tinney and Olsen, 1945	444	16 (3·6%)	141 (31·8%)	117 (26·4%)	274 (61·8%)	170 (38·2%)
Leuallen and Carr, 1955	436	24 (5·5%)	229 (52·5%)	108 (24·8%)	361 (82·8%)	75 (17·2%)
Mestitz, Purves and Pollard, 1958 ..	188	75 (39·9%)	45 (23·9%)	20 (10·6%)	140 (74·4%)	48 (25·6%)

TABLE VI.—THE SUCCESS RATE IN PROVING THE DIAGNOSIS, AS MADE BY ANY MEANS, IN CASES OF PRESUMED TUBERCULOUS PLEURAL EFFUSION

Authors	*Total cases*	*No. proven*	
Gsell, 1930	94	78	(83·0%)*
Frederiksen, 1934	157	41	(26·1%)
Feldman and Lewis, 1946	59	10?	(16·9%)
Maclean, 1948	183	13?	(7·1%)
Kraft, 1949	100	45	(45·0%)
Emerson, 1954	40	18	(45·0%)†
Roper and Waring, 1955	141	51	(36·2%)†
Mestitz, Purves and Pollard, 1958 ..	85	73	(85·9%)†

* It is not clear how this remarkably high figure was reached. Gsell's series consisted of 180 patients; he does not state how the 94 patients analysed in detail were selected. Moreover, 34 of the 94 patients had X-ray evidence of frank pulmonary tuberculosis.

† See text.

Discussion and Conclusions

Even when pleural biopsy is used one-quarter of all patients with pleural effusion may remain without a definite diagnosis (Table V). It is quite certain that a number of patients with tuberculous pleural effusions will not be diagnosed even by needle biopsy (Table VI). Only in the last three papers in this table have patients with frank pulmonary tuberculosis or empyema been excluded.) Full surgical biopsy of the pleura is probably indicated in these patients; indeed Donohoe *et al.* (1958) make it their practice not to use antituberculous drugs in the absence of positive proof of tuberculosis.

TABLE VII.—TO SHOW HOW THE FINAL DIAGNOSES WERE REACHED IN 112 CASES OF PLEURAL EFFUSION IN WHOM THE ELUCIDATION OF THE CAUSE OF THE EFFUSION WAS THE FOREMOST CLINICAL PROBLEM

Diagnosis	*Total*	*Made by*	
		Biopsy	*Other means*
Tuberculous	73	70	3
Malignant	30	20	10
Pyogenic*	9	(7)*	9
	112	(97)*	22

* In 7 cases biopsy showed an acute inflammatory reaction in the pleura.

The following are the most valuable investigations, in addition to clinical examination and X-rays, in a patient who presents with a pleural effusion: (i) Needle biopsy of the parietal pleura, (ii) pleural fluid cytology, (iii) bacteriological examination of the fluid, (iv) tuberculin skin test. If a presumptive diagnosis of tuberculous pleural effusion has to be made we consider that a

positive tuberculin test and a predominantly lymphocytic pleural fluid are necessary.

Summary

In the light of our experience with pleural biopsy we have assessed the value of common aids to the diagnosis of tuberculous pleural effusions. Pleural biopsy is by far the most valuable investigation. The only indirect evidence of value in reaching a presumptive diagnosis is a positive tuberculin test together with a predominantly lymphocytic pleural fluid.

We are grateful to Dr. M. J. Purves for allowing us access to the results in his cases.

REFERENCES

Aborelius, M. (1930): *Svenska lak. sallsk. Handl.*, **56,** 115.
Barnwell, J. B. (1955): in Cecil and Loeb's "Textbook of Medicine," 9th ed., p. 1055. Philadelphia.
Berliner, K. (1941): *Ann. intern. Med.*, **14,** 2266.
Bonilla, J. L. (1942): *Amer. Rev. Tuberc.*, **46,** 59.
Calnan, W. L., Winfield, B. J. O., Crowley, M. F., and Bloom, A. (1951): *Brit. med. J.*, **i,** 1239.
Carstensen, B. (1940): *Nord. Med.*, **8,** 1810.
Chauffard, A., and Gombault, A. (1884): *Bull. Soc. méd. Hôp., Paris,* p. 309.
Close, H. G. (1946): *Lancet*, **i,** 193.
Donohoe, R. F., Katz, S., and Matthews, M. J. (1958): *Ann. intern. Med.*, **48,** 344.
Dunin, T. (1887): *Gaz. hebd. med. chirur.*, **24,** 295.
Eberle, A. J. F. (1949): *Tubercle (London)*, **30,** 146.
Emerson, P. A. (1954): *Brit. J. Tuberc. Dis. Chest*, **48,** 261.
(1957): *Lancet*, **ii,** 674.
Engeset, A., and Lygren, T. (1953): *Nord. Med.*, **49,** 290.
Falk, A. (1950): *Dis. Chest*, **18,** 542.
Falk, A., and Stead, W. W. (1956): *Amer. Rev. Tuberc.*, **74,** 897.
Farber, J. E. (1943): *New. Eng. J. Med.*, **228,** 784.
Feldman, D. J., and Lewis, H. P. (1946): *Med. Clin. N. Amer.*, **30,** 245.
Foord, A. G., Youngberg, G. E., and Wetmore, V. (1929): *J. Lab. Clin. Med.*, **14,** 417.
Forbes, J. (1829): Footnote in his translation of Laennec; London, 3rd edition.
Forgacs, P. (1957): *Thorax*, **12,** 344.
Frederiksen, J. A. (1934): *Ergeb. d. ges. Tuberkforsch.*, **6,** 619.
Gaarde, F. W. (1930): *J. Amer. Med. Ass.*, **95,** 249.
Gelenger, S. M., and Wiggers, R. F. (1949): *Dis. Chest*, **15,** 325.
Grant, I. W. B. (1952): in "Davidson's Principles and Practice of Medicine, 1st ed., p. 134. Edinburgh,
Gsell, O. (1930): *Beitr. klin. Tuberk.*, **75,** 701.
Ives, J. C. J., and McCormick, W. (1956): *J. Clin. Path.*, **9,** 177.
Japhé, F. (1913): *Beitr. klin. Tuberk.*, **28,** 465.
Karron, I. G., and Purves, R. K. (1947): *Amer. Rev. Tuberc.*, **56,** 184.
Königer, H. (1908): "Die Zytologische Untersuchungsmethode." Jena.
Korns, J. H. (1926): *China med. J.*, **40,** 821.
Kraft, J. R. (1949): *Amer. Rev. Tuberc.*, **59,** 259.
LeDamany (1897): *La Sem. méd.*, **17,** 427.
Leuallen, E. C., and Carr, D. T. (1955): *New. Eng. J. Med.*, **252,** 79.
Maclean, K. S. (1948): *Guy's Hosp. Rep.*, **97,** 133.
Magath, T. B., and Feldman, W. H. (1932): *Amer. J. Clin. Path.*, **2,** 199.
Mestitz, P., Purves, M. J., and Pollard, A. C. (1958): *Lancet*, **ii,** 1349.
Mumme, C. (1939): *Med. Klin.*, **35,** 846.
Myers, J. A. (1955): *Arch. intern. Med.*, **96,** 191.
Nassau, E. (1941): *Tubercle (London)*, **22,** 249.

OSHIMA, N., SUZUKI, R., and SUZUKI, K. (1933): *Beitr. klin. Tuberk.*, **83,** 441.
PADDOCK, F. K. (1940): *New Eng. J. Med.*, **223,** 1010.
PAGEL, W., SIMMONDS, F. A. H., and MACDONALD, N. (1953): "Pulmonary Tuberculosis," 3rd ed., pp. 346 *et seq.* Oxford.
PINNER, M., and MOERKE, G. (1930): *Amer. Rev. Tuberc.*, **22,** 121.
ROBERTSON, R. F. (1952): *Brit. med. J.*, **i,** 133.
ROBSON, K. (1952): in Marshall and Perry's "Diseases of the Chest," Vol. 2, pp. 6 and 13. London.
ROPER, W. H., and WARING, J. J. (1955): *Amer. Rev. Tuberc.*, **71,** 616.
SILBERSCHMIDT, P. (1924-25): *Beitr. klin. Tuberk.*, **60,** 128.
SKAGGS, J. T., and SMILEY, G. W. (1955): *Amer. Rev. Tuberc.*, **72,** 647.
SPRIGGS, A. I. (1957): "The Cytology of Pleural, Pericardial and Peritoneal Fluids." London.
THOMPSON, B. C. (1947): *Tubercle (London)*, **28,** 229.
TINNEY, W. S., and OLSEN, A. M. (1945): *J. thorac. Surg.*, **14,** 248.
TOMITA, Y. (1939): *Beitr. klin. Tuberk.*, **92,** 538.
VAIZEY, J. M., and PERRY, K. M. A. (1940): *Lancet*, **i,** 1120.
WIDAL, RAVAUT (1900): *Compt. rend. Soc. biol., Paris*, **52,** 648.
WILLIS, H. S., and CUMMINGS, M. M. (1952): "Diagnostic and Experimental Methods in Tuberculosis." 2nd ed. Springfield.
WYNN-WILLIAMS, N., and SHAW, J. B. (1955): *Tubercle (London)*, **36,** 74.
YOUNG, R. A., and BEAUMONT, G. E. (1950): In Price's "Textbook of the Practice of Medicine." 8th ed., p. 1311. London.
ZINNEMAN, H. H., JOHNSON, J. J., and LYON, R. H. (1957): *Amer. Rev. Tuberc.*, **76,** 247.
ZÜST, F. (1946): *Schweitz. Ztschr. f. Tuberk.*, **3,** 52.

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THE EFFECTS OF PREDNISOLONE ON CHRONIC DRUG RESISTANT PULMONARY TUBERCULOSIS IN KENYA AFRICANS

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It was early shown that cortisone and corticotrophin led to the rapid progression of experimental tuberculosis in laboratory animals (Hart and Rees, 1950; Spain and Molomut, 1950) and the reactivation of quiescent pulmonary tuberculosis in man (Popp *et al.*, 1951; Kleinschmidt and Johnstone, 1951; American Trudeau Society, 1952). This was rapidly followed by many reports that, provided adequate chemotherapy was also given, no harm resulted, and that some patients might even benefit by the combination (Houghton, 1954; Climie *et al.*, 1956; Cochran *et al.*, 1956; Harris, 1957).

Certain indications are now appearing for the administration of the cortisone group of drugs in addition to adequate anti-tuberculous drugs. Drug hypersensitivity was an early one (Houghton, 1954). Exhaustion after major operations (Edge, 1956), severe toxæmia in acute disease (Bland, 1957; Harris, 1957), and in tuberculous meningitis if the toxæmia is severe or if little progress is being made (American Trudeau Society, 1957) are others. It is probably also of use in pleural and pericardial tuberculous effusions, in endobronchial tuberculosis in children (American Trudeau Society, 1957) and in glandular and laryngeal tuberculosis. When the combination is used in previously untreated cases of pulmonary tuberculosis the improvement appears to be more rapid than in those treated without the addition of cortisone, but the end result is probably the same (Tuberculosis Society of Scotland, 1957). In this hospital the combination seems to have been life-saving in pulmonary and meningeal tuberculosis when the patient has been severely toxic, even almost moribund.

It has usually been said that the cortisone group of drugs should only be added to the anti-tuberculous drugs if the organism is fully sensitive to these drugs (American Trudeau Society, 1957). However, there have been many trials with cases of chronic pulmonary tuberculosis and without doubt some of these were drug resistant. Advanced chronic tuberculosis, resistant to chemotherapy and beyond the scope of surgery, has been regarded as an indication for the combined therapy (Turiaf and Marland, 1955). Shubin and Heikin (1956-57) treated thirty patients with prednisolone and anti-tuberculous drugs. Eighteen showed no change, two became worse and twelve with moderate to marked laboratory resistance to the anti-tuberculous drugs became much less resistant, radiologically clearer, and the sputa became and remained negative. They had shown no radiological change and had had persistently positive sputa for at least one year prior to this treatment.

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Plan of Trial

Nine adult patients, the first suitable ones to be seen, were selected. Seven were male and two female; one of the Kipsigis tribe, the other Kikuyu. They all had chronic, fibro-caseous, cavitating, bilateral pulmonary tuberculosis. Two had had the disease for two years, two for three years, three for five years, one for six years and one for seven years. They had all had various courses of streptomycin, para-aminosalicylic acid (PAS) and isoniazid (INAH). They were all markedly resistant to these drugs and were either at a standstill or deteriorating when this trial commenced. They were all treated in hospital and given 150 mg. of INAH and 6 gr. of PAS at twelve-hourly intervals. They were also given prednisolone (Deltacortril, Pfizer Ltd.) 5 mg. every six hours for seven days, and then 2·5 mg. every six hour for six months. After the six months the prednisolone was gradually discontinued over two weeks and no untoward symptoms were seen on its cessation. Each month they were examined clinically, weighed, blood pressures were recorded, the urine was examined, an E.S.R. (Westergren) measured, sputum smears were examined for acid-fast bacilli and a chest radiograph was taken. After three and six months the sensitivity tests were repeated. The technique for sensitivity testing was that used by the Medical Research Council (1953).

Results

Within a day or two all nine patients felt very much better and this subjective improvement was maintained. Their appetite improved and their cough and sputum lessened considerably.

The weight increased in eight patients and remained stationary in one. The average weight gain was 11·7 lb. in the six-month period, the maximum being 28 lb. This was not entirely due to the improved diet from being brought into hospital, for four had been in the hospital for some months before commencing prednisolone, and yet were among those making the largest gains.

The sedimentation rate fell markedly in three patients, was normal and remained so in one, and was raised and remained so in the other five.

The sputum remained consistently positive at every examination in all nine patients.

In the months preceding the trial six of the patients were steadily deteriorating radiologically and three were at a standstill. During the trial one deteriorated steadily as before, one that had been deteriorating improved considerably, and seven remained unchanged. Thus there was radiological evidence of the patients' improvement if only because the deterioration did not continue. The one that improved radiologically had had some acute spread to the left base in the preceding six months, and the long-standing right apical disease had worsened (*Fig. 1). After two months of prednisolone the right upper zone was improving, and after three months most of the right apical disease had cleared and the left basal disease was clearing (Fig. 2). No further improvement occurred.

* The figures referred to in the text appear on Plate XIV.

FIG. 1.—X-ray of chest showing extensive disease in both lungs.

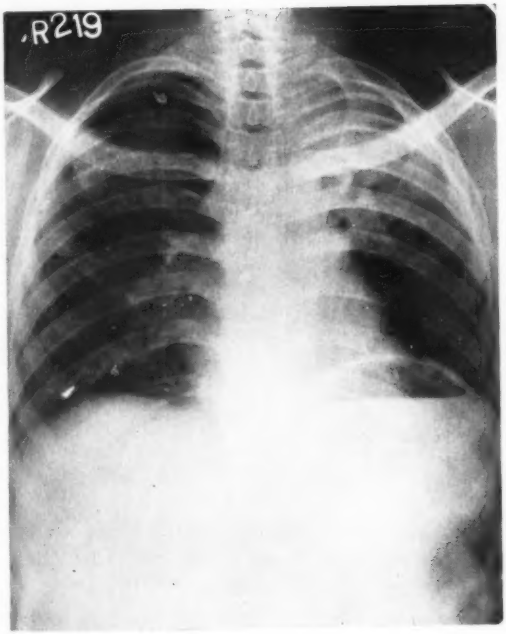

FIG. 2.—X-ray of chest showing good evidence of resolution following five months of Prednisolone therapy in addition to the anti-tuberculous drugs.

To face p. 96

The sensitivity tests to INAH showed the organisms to be originally markedly resistant, all but one producing confluent growth up to 50 micrograms per ml. They were all catalase negative. No change in the sensitivity nor in the catalase activity was seen.

All were originally markedly resistant to PAS, mostly with resistance ratios (Medical Research Council 1953) of 64 or more. No change in sensitivity was seen.

Eight of the patients showed no change in their streptomycin sensitivities, but the ninth showed a remarkable change. Originally she was completely insensitive, producing confluent growth at 64 microgrammes per ml., so that the resistance ratio could not be stated. After three months of prednisolone her organism was more sensitive than H37RV with a resistance ratio of 0·5 This was repeated and confirmed and again at six months the organism was found to be sensitive. In order to follow this to its logical conclusion, after the trial and in spite of many previous courses of streptomycin, this patient was given streptomycin 1 g. daily and PAS 18 g. daily. After four months of this treatment her sputum was persistently smear and culture negative. Not since the disease had been discovered had this been so. There was also radiological improvement, a long-standing left basal cavity having closed.

On review of all the patients three months after the prednisolone had been stopped the gains that had been made had also been maintained. The one patient who had continued to deteriorate throughout the trial died six weeks after it had finished. It is not considered that the prednisolone had anything to do with this.

Side Effects

All nine patients showed rounding of their faces. Two complained of blurring of vision for most of the six months; this disappeared when the prednisolone was stopped. No hirsutes was seen and the blood pressure readings were consistently normal. Glycosuria was never demonstrated. No pitting œdema was ever found.

Discussion and Conclusions

The cortisone group of drugs are said to exert their deleterious effect on tuberculosis by suppressing the normal inflammatory reaction and by inhibiting the formation, or facilitating the destruction, of granulation tissue. That this could be an advantage when adequate anti-tuberculous drugs are given was pointed out by Houghton (1954), and clinical experience has substantiated this. Why these drugs should also be of use when the chemotherapy is inadequate it is difficult to say. Our knowledge of their effects is clearly incomplete.

It is known that in the late stages of chronic pulmonary tuberculosis adrenocortical hypofunction occurs. This has been shown by the diminished excretion of 17-ketosteroids and 11-oxysteroids in such patients. It is possible that some of the symptoms such as fatigue, weakness and anorexia are due to this, and that the corticosteroids are a replacement therapy, and therefore ameliorate these symptoms. This has been elaborated by Katz *et al.* (1955), who described nine cases who had all had various courses of chemotherapy and

who were all, at least partially, resistant to the anti-tuberculous drugs. The addition of hydrocortisone caused considerable symptomatic improvement in seven, and in no case was there any radiographic deterioration. There was a diminution in the number of tubercle bacilli excreted, but they did not see sputum reversal as did Shubin and Heiken (1956-57). However, this does not explain the occasional radiographic improvement nor the occasional sensitivity changes such as were seen in one patient in this small trial, and much more frequently by Shubin and Heiken (1956-57). Indeed, if resistance is genetically determined and due to the multiplication of resistant mutants, as is generally believed, it is difficult to see why cortisone should in any way affect this.

It is concluded that, even when considerable drug resistance exists and when the chemotherapy is therefore ineffective, or only partially effective, the addition of prednisolone may still be justified. It seems to be safer than would theoretically be expected. It produces considerable subjective improvement in what is otherwise an inevitable, progressive deterioration. It may occasionally lead to unexpected improvement of lasting importance, such as in the patient described who regained her sensitivity to streptomycin and was thus enabled to attain a negative sputum culture for the first time in the four years that she had been known to have the disease.

Summary

Nine patients with chronic, drug resistant, pulmonary tuberculosis were given prednisolone in addition to INAH and PAS. All showed rapid and considerable clinical improvement. One showed marked radiological clearing and one regained her sensitivity to streptomycin and became culture negative after further treatment. None became sputum negative as a result of the addition of the prednisolone. It is concluded that prednisolone has a definite place in the treatment of chronic pulmonary tuberculosis, even if the covering chemotherapy is not fully effective because of drug resistance.

I should like to thank Dr. John Carman and Messrs. Pfizer Ltd. for the generous supplies of prednisolone (Deltacortril), and Mrs. Peak for the radiographs.

REFERENCES

American Trudeau Society (1952): *Amer. Rev. Tuberc.*, **66**, 254.
(1957): *ibid.*, **76**, 708.
Bland, C. V. (1957): *Brit. J. Tuberc. Dis. Chest.*, **51**, 379.
Climie, H., Beven, G., and Sims, S. R. (1956): *ibid.*, **50**, 265.
Edge, J. R. (1956): *Tubercle (Lond.)*, **37**, 166.
Harris, L. H. (1957): *Brit. J. Tuberc. Dis. Chst*, **51**, 98.
Hart, P. D'Arcy, and Rees, R. J. W. (1950): *Leancet* **2**, 391.
Houghton, L. E. (1954): *ibid.*, **1**, 595.
Katz, S., McCormick, G., Shea, J., Schmidt, W., Leonard, J., Chambers, J., and Gimble, A. (1955): *Trans. 14th. Conf. on Chemother. Tuberc., Veterans Admin. Army, Navy*, 299.
Kleinschmidt, R. F., and Johnstone, J. M. (1951): *Ann. intern Med.*, **35**, 694.
Popp, C. G., Ottoson, P., and Brasher, C. A. (1951): *J. Amer. med. Ass.*, **147**, 241.
Shubin, H., and Heiken, C. A. (1956-57): *Antibiotics Annual*, 437.
Spain, D. M., and Molomut, N. (1950): *Amer. Rev. Tuberc.*, **62**, 337.
Tuberculosis Society of Scotland (1957): *Brit. med. J.*, **2**, 1131.
Turiaf, J., and Marland, P. (1955): *Bull. Soc. méd. Hôp. Paris*, Nos. 29, 30 and 31, p. 1174.

Brit. J. Dis. Chest (1959) **53**, 99.

A TUBERCULIN SURVEY IN THE ISLAND OF MONTSERRAT, BRITISH WEST INDIES

By Richard A. S. Cory

From the Pan American Sanitary Bureau, Regional Office of the World Health Organisation, Washington

Introduction

This survey was conducted on behalf of the Pan American Sanitary Bureau, Regional Office of the World Health Organisation for the Americas, between November 27 and December 6, 1957, with the object of determining the needs of the island of Montserrat for a BCG mass campaign.

Montserrat is a small, very mountainous West Indian island belonging to the group known as the Leeward Islands. With Antigua and St. Nevis it constitutes an inverted triangle, 32½ square miles in area, with Antigua about 27 miles to the north-east and St. Nevis 33 miles to the north-west.

Geologically it is believed to be entirely volcanic. There are three groups of mountains of which those in the south rise to over 3,000 feet. Between these and the mountains to the west there is a high saddle of land lying at about 1,200-1,500 feet which is almost entirely given over to agriculture.

Several hot sulphur springs bear witness to the volcanic origin of the island.

Heavily wooded mountain slopes above 1,500 feet explain the abundance of little streams. For a West Indian island the climate is unusually cool, and it is said that there is no indigenous malaria.

Discovered by Columbus in 1493, the island was named by him after a mountain near Barcelona. It was first colonised by the English in 1632, only to be captured by the French in 1664. Restored to England in 1668, it was largely populated by Irish in the next half-century, and today many of the names of the inhabitants are Irish.

In 1782 it was again captured by the French, to be ceded back to England two years later. Since 1784 it has been a British colony, becoming recently a member of the West Indian Federation.

The early European planters, who cultivated cotton and sugar cane, introduced slave labour as elsewhere in the West Indies, and today the population is almost entirely coloured, though there still remain a few white families and business men, probably under 1 per cent. of the total population. Sea Island cotton gradually took over from sugar cane, but in the middle of the nineteenth century the lime became an important product. This latter has now largely disappeared as a result of disease making its appearance among the trees.

Today Montserrat produces only some cotton, sugar, rum and a certain amount of vegetables, which latter are largely marketed in the neighbouring island of Antigua.

Financially it is a poor island, though a great number of the people—

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particularly in the northern half—own and work their individual pieces of land.

Plymouth, the capital town, with a population of about 4,000, is located on an open roadstead in the south-west. The overall population of the island is probably somewhat under 14,000. In the last few years some 3,000 of the adults have emigrated to England in search of more remunerative work. How many of these will return—some with tuberculosis—is uncertain, but the homeward drift has not yet begun.

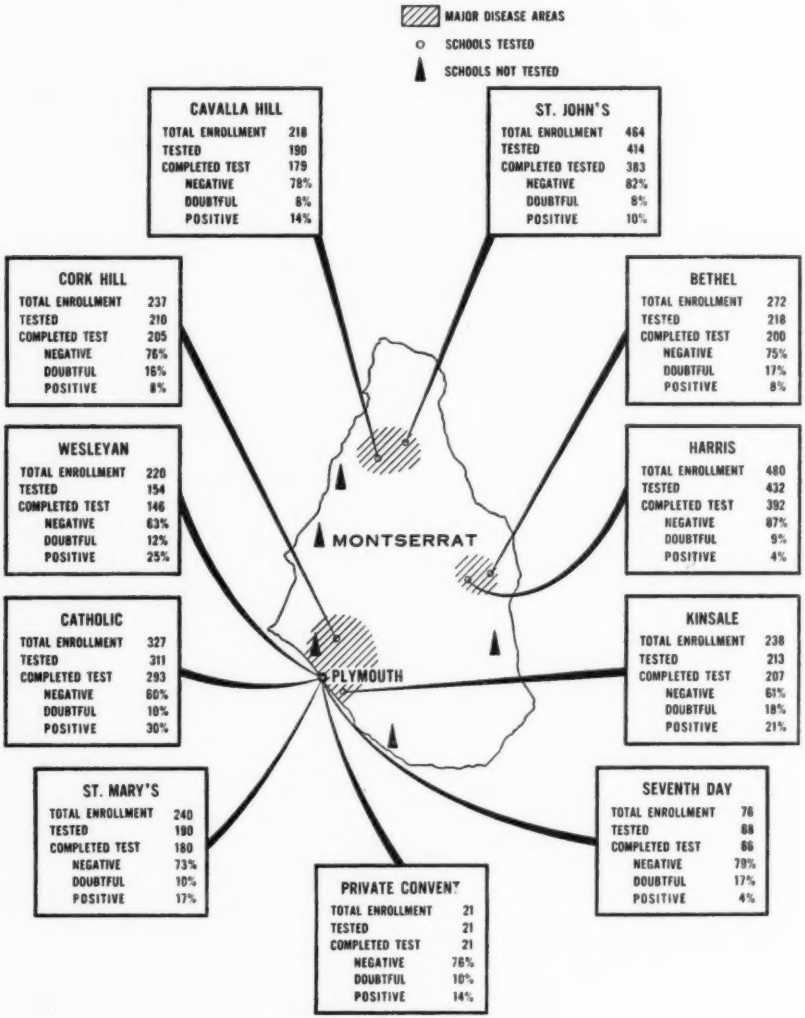

FIG. 1.—Montserrat, B.W.I.

Outside communications, as with all of the smaller West Indian islands, are poor. The only really regular means of transport was opened up recently by the Leeward Islands Air Transport, a subsidiary of British West Indian Airways. Heavy material such as the cotton has, of course, to be transported by sea.

Owing therefore to the island's relative isolation there is but little travel between it and the other units of the West Indies. The chances of outside cases of tuberculosis bringing in active infection can consequently be regarded at the moment as negligible.

The medical service, which consists of only three doctors for the whole island, is essentially the province of government, though the doctors are allowed outside practice. There is a seventy-bed hospital in Plymouth, and this provides excellent accommodation for about twelve cases of tuberculosis, but it is unfortunately poorly patronised by the existing cases.

No X-ray facilities are available in the whole island, and as a result early diagnosis and follow-up are quite out of the question.

The problem of tuberculous infection in this survey, therefore, had to be assessed entirely on the reactions to tuberculin of the individuals tested.

In 1957 there were five deaths from tuberculosis. Allowing for a population of 14,000, this gives a death rate of 35 per 100,000.

In December 1957 there were twenty-six known cases of tuberculosis—only one of whom was in hospital. A few of these are certainly arrested, but accurate information on the majority is completely lacking.

During the two years 1956-57, 58 children under the age of 1 year died, 13 of these as a result of chest conditions (bronchitis or broncho-pneumonia). Whether any of these were really due to tubercle is not known, but at least 3 of them were contacts of diagnosed cases.

In the survey the people of the island were extremely co-operative, and the amount of work done was limited only by the time available.

A total of 2,924 individuals received a single Mantoux test using 5 tuberculin units of Purified Protein Derivative as the dose. Of this total, 192 individuals, or 6·5 per cent., failed to return for reading of the reaction, leaving 93·5 per cent. of the original number examined as having completed the test. This is a gratifyingly high rate. The overall total was made up as follows:

Adults (between 16 and 80 years)	333
Adults (schoolteachers only) ..	65
Children in eleven schools ..	2,421
Children (birth—15 years) not at school	105
Total	2,924

Of the eleven schools examined, ten were elementary schools normally taking children between the ages of 5 and 15 and one was a small, private convent-school dealing with similar age groups. Unfortunately, the only secondary school was closed for the holidays and could not be investigated. This was the only school omitted in the Plymouth area.

The group of adults, apart from the school teachers, was completely heterogeneous and comprised doctors, nurses, hospital patients and orderlies,

prisoners, police, government servants, paupers and various adults who came for tests either to the health centre or to the schools. They came from virtually all districts of the island, and represented all the social levels in Montserrat.

Tuberculin reactions have been graded as follows:

Negative	No trace of reaction
+	Minute nodule at site of injection, often undoubtedly non-specific; under 5 mm.
+	Œdema of 5-7 mm.
+ +	Œdema between 8 and 15 mm.
+ + +	Œdema between 15 and 20 mm.
+ + + +	Greater than 3 plus or necrotic.

On the tables these reactions have all been charted separately, but the ± group can be regarded as debatable, and many authorities might consider such reactions as essentially negative when using them as a basis for BCG inoculation. Most reactions were read after 48 hours, though some were read at 72 hours.

The Survey and Findings

Of the overall total of 2,924 individuals originally tested, 1,880 were completely negative, a further 310 were questionable, while 542 were frankly positive to tuberculin; 192 failed to complete the test.

Of the positive group, 84 individuals, or 11·7 per cent. of that group, showed a very strong reaction.

Deducting the 192 persons who failed to return for reading from the original number tested, a total of 2,732 completed the test.

In nearest percentages, therefore, of those completing the test the figures given above show the following:

Table 1.—Reactions on all Individuals completing the Test (Total 2732)

Reaction	*Total number*	*Percentage*
Negative	1880	69
Doubtful	310	11
Positive	542	20
Total	2732	100

It can be seen, therefore, that slightly under 70 per cent. of the population of the island have never had a primary infection with tubercle bacilli. If the doubtfuls are included in this group, the figure rises to 80 per cent.

Twenty per cent. are definitely infected, and at least one-tenth of these show severe reactions, suggesting that some of them are harbouring active or potentially active lesions.

This point is important and should be borne in mind for future investigation, as it is highly possible that from these strong reactors may arise future infectious cases.

A separate table has been prepared (Table II) to show the reactions encountered amongst the heterogeneous group of adults previously mentioned. It is a small group but is nevertheless fairly representative of the state of affairs generally obtaining in the island, as the persons in it came from widely separated areas, though admittedly most of them were from the capital city of Plymouth.

TABLE II.—ADULTS, BETWEEN 16 AND 80 YEARS OF AGE (Total 333) (303 completed the test)

Age group	*Intensity of tuberculin reaction*						*Failed to return*	*Totals*
	Negative	±	+	++	+++	++++		
16-24	29	13	23	14	4	6	11	100
25-34	24	2	20	10	6	1	5	68
35-44	7	5	23	14	4	6	6	65
45-54	7	6	14	5	4	4	3	43
55+	19	8	16	8	1	0	5	57
Totals	86	34	96	51	19	17	30	333
	28	11	32	17	6·3	5·7	–	100
%of 303 completing the test	39		49		12			
	39		61					

In Table II are also shown the percentages negative, doubtful and positive in the 303 adults who completed their tests. It will be seen that only 28 per cent. of all the adults were completely negative, 11 per cent. were doubtful, and 61 per cent. were clearly positive. Table II also shows that of the 303 adults completing their test, 36 (12 per cent.) gave a very strong reaction to 5 tuberculin units.

The school teachers form a small but interesting group, comprising as they do practically all those teaching in the eleven schools examined (Table III).

It will be seen that the negatives in this group form a higher percentage than in the general adult group. In addition we did not find a single strong reactor among the 64 teachers who completed the test.

Finally, the children have now to be considered and compared with the findings in adult groups.

Although the vast majority were reached by mass school testing, we were able to obtain some results on a group who were either too young to be at school, or who for some reason were away from school at the time when the test was done. In this group we tested 105 children, varying from about 2 months to 15 years of age.

Table IV shows the results broken down by age groups. Twelve of these children failed to complete the test, leaving 93 for analysis.

It will be seen that from 77 to 85 per cent. of the group were negative, while 15 per cent. were definitely positive. There were 3 children with strong reactions in this group, and one of them was less than 5 years old.

TABLE III.—SCHOOL TEACHERS (Total 65)

Reaction to 5 tuberculin units ..	*Intensity of tuberculin reaction*						*Failed to return*	*Total*
	Negative	±	+	++	+++	++++ *Necrotic*		
Number	31	6	17	10	0	0	1	65
% of those completing the test	48·5	9·5	42					
	58							

TABLE IV.—CHILDREN NOT AT SCHOOL (105 tested; 93 completed test)

Age group	*Intensity of tuberculin reaction*						*Failed to return*	*Totals*
	Negative	±	+	++	+++	++++ *Necrotic*		
0-1½ yr.	8	0	0	0	0	0	2	10
1-1½ yr.	9	1	0	0	0	0	0	10
2-5 yrs.	38	0	1	0	1	0	2	42
6-12 yrs.	10	0	2	2	1	1	0	16
13-15 yrs.	7	6	4	2	0	0	8	27
Totals	72	7	7	4	2	1	12	105
% of those completing the test	77	8	15					
	85							

One very striking feature presented itself here. Six children under the age of 5 years lived in a yard, where we found them being cared for by a "known" case of tuberculosis who had refused to remain in hospital. All these six children were completely negative, and the "known" case herself showed a doubtful reaction. Her sputum had never been proved to be positive, and she had not been X-rayed. It seems likely that she was not a case of tuberculosis.

Reference should now be made to the largest and most important group of all, the children in the elementary schools. Eleven of these schools were visited, and tests were carried out on all the children found present. A total of 2,421 such children were tested, and Table V shows the overall results.

As the schools were too numerous to be covered in the time available, a chart of the island was prepared (Fig. 2) and on it are pin-pointed the known cases, as well as the locations of the deaths occurring within the last two years, and certified as having been due to pulmonary tuberculosis.

Having established from this map that two particular areas of the island, Plymouth in the south-west (seven schools tested) and St. Johns in the north (two schools tested), seemed to account for most of the known cases and deaths,

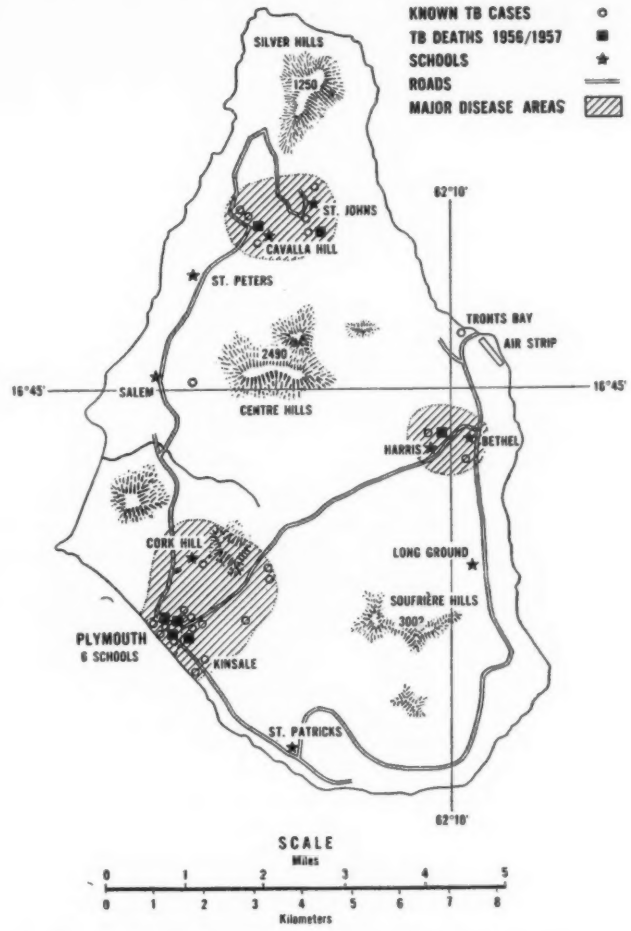

FIG. 2.—School Distribution and Results of Mantoux Test.

an attempt was made to test all the schools in these two areas. A third small group of cases in the east, at Harris, led to the inclusion of two more schools in this area, bringing the total of schools examined to eleven.

In the Plymouth area the secondary school, which had closed for the holidays, could not be tested. With this exception, all the schools in the suspicious areas were examined. Four other schools had to be omitted from the survey as there was not enough time to cover them. The areas in which they were situated, however, showed only one known case, and no known tuberculous deaths.

The total enrolment of children in the eleven schools examined amounted

TABLE V.—COMPREHENSIVE TABLE OF ALL CHILDREN TESTED IN ELEVEN SCHOOLS (Total 2421)

Age group	*Intensity of tuberculin reaction*						*Failed to return*	*Totals*
	Negative	±	+	++	+++	++++ *Necrotic*		
0-4 yrs.	11	1	0	0	0	0	1	13
5-9 yrs.	1006	109	64	14	14	7	61	1275
10-14 yrs.	653	150	164	21	18	4	78	1088
15-19*	21	3	8	2	2	0	9	45
Totals	1691	263	236	37	34	11	149	2421
% completing the test	74	12	14					
	86							

* No children older than 16 in these schools.

to 2,793 and of these 2,421 were originally tested, 149 of whom failed to complete the test, leaving a total of 2,272 for final analysis or 94 per cent. of those tested.

Of those whose tests were completed, 74 per cent. were negative, 12 per cent. were doubtful and 14 per cent. were definitely positive. There were 45 individuals in the whole group who reacted strongly, and 21 of these were under 9 years of age.

As the total school enrolment throughout the whole island amounts to 3,432, this survey was able to complete the findings on 66 per cent. of all the school children in Montserrat, in spite of the fact that five schools containing 639 pupils had to be excluded.

TABLE VI.—A COMPARISON BETWEEN URBAN AND RURAL SCHOOL CHILDREN WITH REGARD TO THEIR REACTIONS (2,272 CHILDREN COMPLETING TEST). Urban, 6 schools; Rural, 5 schools

Age group	*Tuberculin reaction*						*Totals on which percentages are based*
	Negative		*Doubtful*		*Positive*		
	Urban	*Rural*	*Urban*	*Rural*	*Urban*	*Rural*	
0-4 yrs.*	87%	100%	13%	0%	0%	0%	12
5-9 yrs.	77%	87%	10%	8%	13%	5%	1214
10-14	51%	74%	16%	14%	33%	12%	1010
15-19†	70%	44%	0%	19%	30%	37%	36

* Figures in 0-4 and 15-19 age groups are too small for significant information.

† No children older than 16 in these schools. Percentages are shown, and overall age-group numbers.

There was a fairly marked difference in the reactions shown by children in the urban schools (Plymouth) when compared with those in rural areas,

and Table VI has been prepared to bring out this point, which has been noted in similar surveys in other countries. In the 5-9 and 10-14 age-groups, there is

TABLE VII.—INDIVIDUAL SCHOOLS SHOWING RESULTS IN URBAN AND RURAL UNITS
(Percentages given are to nearest round number)

	Name of school	*Number tested and completed*	*Tuberculin reactions*					
			Negative		*Doubtful*		*Positive*	
			No.	%	*No.*	%	*No.*	%
URBAN	Covent, private	21	16	76	2	10	3	14
	Wesleyan	146	91	63	18	12	37	25
	Catholic	293	175	60	31	10	87	30
	Seventh Day Adventist ..	66	52	79	11	17	3	4
	St. Mary's	180	132	73	17	10	31	17
	Kinsale	207	126	61	37	18	44	21
RURAL	Cork Hill	205	156	76	32	16	17	8
	Cavalla Hill	179	140	78	15	8	24	14
	Bethel	200	150	75	34	17	16	8
	Harris	392	341	87	34	9	17	4
	St. John's	383	312	82	32	8	39	10
	Totals	2272	1691	—	263	—	318	—
	Percentages	100%	74%		12%		14%	

Note the appreciably lower positive rates in the rural schools.

a significantly higher proportion of positive reactors in urban schools than is to be found in their rural counterparts.

The 15-19 group, however, shows a reversal of this finding due to the fact that in one school (St. Johns) there were 4 positive reactors out of the 5 pupils in the school in this age-group. This particular school serves a part of the northern area where it was noted that 4 cases of tuberculosis had occurred.

Table VII shows the names of the individual schools, the numbers completing tests in each, and the results, school by school. It also differentiates between the urban and the rural schools.

From this table it can be seen that three schools in the urban area show more than 20 per cent. of their pupils with a positive reaction. The Catholic school rises as high as 30 per cent. This is believed to be the result of contact, in the school, with a girl who was found to be an active case with a positive sputum. No rural school runs as high as a 15 per cent. positive rate, though Cavalla Hill and St. Johns—both in the suspicious area in the north—have rates of 10 per cent. or somewhat over.

Harris, Bethel and Cork Hill in country areas where there have been few known cases, run infection rates of 8 per cent. or less.

On Map 2 have been charted all the salient features of the survey, and reference to it will give the results found in all the areas tested.

Summary

The survey appears to have established the following facts:

Tuberculous infection in adults in Montserrat is fairly widespread (61 per cent.).

In children it is low, rising from 4 per cent. in some rural schools to as much as 25 to 30 per cent. in the urban schools.

Rural schools in areas where known cases have occurred show a higher infection rate than those in " clean " areas.

About one-tenth of the positive reactors in the schools show strong reactions, suggesting that at least some of them have active or potentially active diseases.

There are no facilities for X-ray work, and laboratory facilities exist only for sputum examination by smear. As a result of this, an adequate case finding programme is quite impossible at present.

There is a very satisfactory ward for isolation of tuberculous cases, but the people refuse to remain in hospital after a month or two on drugs, as a result of their having begun to feel better.

Brit. J. Dis. Chest (1959) **53**, 109.

THE TRAINING OF THE GREATEST OF CHEST PHYSICIANS: LAENNEC

By E. Ashworth Underwood

Director of the Wellcome Historical Medical Museum and Library

Part I: Nantes

On the auspicious occasion of the change in the title and scope of this Journal, it may be of interest to its readers to hear something of the life of the greatest of all chest physicians, René Théophile Hyacinthe Laennec (1781-1826). Every medical student knows—or should know—that Laennec invented the stethoscope, and that in 1819 he described it, together with the clinical investigations in which he had used it, in his great book, *De l'auscultation médiate*. Probably only those who are really interested in the subject realise that the sub-title of that book was *Traité du diagnostic des maladies des poumons et du cœur, fondé principalement sur ce nouveau moyen d'exploration*, and that in it Laennec revolutionised the subject, introduced new terms, and made substantial advances in pathology. In the second edition, published in the year of his death, the description of the physical signs has become completely modern, and the work stands as one of the greatest contributions, if not the greatest single contribution, to a subject ever made by one individual. This aspect of Laennec's work has been frequently described and discussed, among others by Dr. Clifford Hoyle in a lecture, published in this Journal, given fifteen years ago. All this *ought* to be well known. But, on the other hand, very few will be familiar with the training and early struggles of Laennec, and this seems a fitting occasion to give a brief outline of that formative period of his life.

Laennec was born at Quimper in Brittany on February 17, 1781. He was the eldest child of Théophile Marie Laennec, an able lawyer, but unfortunately a very unpractical man. He was a poet of some ability, and this gift did not, in his case, mix well with the law. To him and Michelle Guesdon, his first wife, two other children were born. The elder of these, Michel Jean Bonaventure—familiarly known as Michaud—was almost as brilliant as his brother Théophile. The mother died on November 15, 1786, in a fourth confinement, and the father was faced with a difficult situation. By the following January he had persuaded his brother Michel, then rector of the parish of Elliant, to take the boys. But a year later Michel was appointed canon of Tréguier, and, being unable to continue with the care of the boys, he wrote to another brother, Guillaume, suggesting that he might accept the responsibility. It thus came about that, after a few months at their home at Quimper, Théophile and Michaud, then aged 7 and 6, travelled by sea in the care of the captain of a coasting-vessel, from Quimper to Nantes, where they arrived on May 15, 1788.

Guillaume François Laennec (1748-1822), the uncle to whose care the father had entrusted his two sons at this early age, deserves to be better known.

(*Received for publication October* 30, 1958)

A native of Quimper, he studied medicine in Paris, took his doctorate at Montpellier, and then studied for two years in England. He then returned to practise medicine in his native town. In the year in which Théophile Laennec was born Guillaume became engaged to a young lady of 16. Her family agreed to the marriage on condition that he settled in Nantes or in Rennes. Guillaume chose Nantes, the first port of Brittany, and the seat of an ancient university. After he had settled there he discovered that, in order to receive permission to practise in the city, he would have to matriculate and go through all his studies again. The aid of Parliament had to be invoked, and it was not until 1785 that the Nantes Faculty finally capitulated to a specially written thesis. Guillaume now rendered a service to the Faculty, and as a result he was elected Rector of the University of Nantes for the year ending November 1788. He was therefore holding that office when the two boys passed under his care. (Figs. 1 and 2.)

Guillaume, a talented classical scholar, undertook the education of his nephews for a few months, and he then sent them to a school. In the following year the Revolution broke out, and in the next few years young Laennec saw bloody events. During the Terror 3,000 persons were executed in the city—at first by the guillotine, and when this proved too slow, by the method of drowning referred to as the " noyade de Loire," and finally by massed artillery. Within the next few years he saw fifty heads severed by the guillotine outside the windows of his uncle's house. In 1793 Nantes was attacked by the Grande Armée of the Vendeans, and the two boys were sent to make dressings and to assist their uncle at the Hôtel-Dieu. As a result of these events at least nine military hospitals—*hôpitaux ambulants*—were opened in Nantes, and to one of these, *la Paix*, Guillaume was appointed chief physician. Others were *l'Unité* and *la Fraternité*, and each had 300 to 400 beds. During this time young Théophile had made excellent progress in languages, and he had shown himself to be a budding poet. Guillaume, with his brother's example in mind, frowned somewhat on this dissipation of energy. About this time there began the unending series of letters from Théophile to his father asking for a little money to buy books. Théophile at first wanted to be an engineer, but his uncle's stimulus soon turned him to medicine.

Laennec's medical studies started on September 29, 1795, when he was appointed " chirurgien de 3^{e} classe " in the military hospitals. He was then aged 14 years 7 months. The arrangement at that time was that these junior apprentice surgeons worked for part of the day in a military hospital and received a small stipend. During the rest of the day they studied at the medical school. Laennec was sent to *la Paix*, where he was under his uncle's supervision. But in the following year that hospital was closed, and Laennec went to *la Fraternité*, where he began to learn blood-letting, the dressing of wounds and minor surgery.

The medical school at Nantes deserves some comment. The teaching of medical students had been undertaken jointly by the Faculté de Médecine and the École de Chirurgie, but these two institutions were simultaneously suppressed in 1793. But there were two active seats of medical instruction. At the Hôtel-Dieu Luc Augustin Bacqua had been conducting official courses in anatomy

and surgery. He was a first-class anatomist, and he had gained wide fame because of the fact that, in these pre-anæsthetic days, he had performed two successive Cæsarean sections successfully on the same woman. About 1790 a private school had been started by Jean Baptiste Augustin Darbefeuille (1756-1831), who held the chair of pathology and therapeutics. About the time of the suppression of the Faculty and the École de Chirurgie, Darbefeuille was appointed chief surgeon to the Hôtel-Dieu (or, the Temple de l'Humanité as it was called at that time), and about the same time Bacqua became chief resident surgeon. Darbefeuille now straightway transferred his school to the Hôtel-Dieu and amalgamated it with that of Bacqua, so that there was practically no break in medical teaching. The arrangement was that Darbefeuille would teach physiology, pathology and therapeutics; Bacqua would be responsible for anatomy and surgery; and the second resident surgeon, Pierre Desray, would teach osteology and minor surgery, and would act as demonstrator in anatomy.

For beginners the course at the Hôtel-Dieu really started on July 20, and the next two months were spent in studying osteology. Laennec was probably taught this by his uncle, since he did not commence until September. For all except first year students the academic year began on September 20. The next five months—until February 19—were spent on the study of anatomy, and the next two—until about the middle of April—were devoted to "médecine opératoire." This ended the first semester. The second semester was supposed to take up the remaining five months in the year, during which physiology, pathology and therapeutics were taught. But for all except first year students, and those who desired some revision, the period from July 20 to September 19 seems to have been a holiday. In addition, during the two months April 20 to June 19, blood-letting, bandaging and the uses of instruments were taught.

Laennec entered into these studies with great enthusiasm, and he also extended his studies in languages. He took a course in Greek—repeated often in later years—with the desired end of being able to read Hippocrates easily in the original. Even by the end of the first year of his medical studies he was speaking Latin with a rare perfection. He also extended his studies in natural history, increased his collection of insects, flowers and minerals, and became attached to François le Meignen, well-known mineralogist who was the director of the apothecaries' herb garden at Nantes.

Laennec began his second year with Bacqua's course of anatomy as usual. But before three months had passed the authorities had decided that they wanted their chief surgeon—namely, Darbefeuille—to be such in reality without any competitor; Bacqua was therefore dismissed on the pretext that his term of office had expired, and from that moment he disappears from the pages of history. Early in 1797 Laennec lost his post as a surgical officer. The authorities had decided to reduce the number, and as a junior Laennec had to lose his job and the small stipend attached to it. At the end of his second year he returned to his home at Quimper (July 8, 1797) after an absence of nine years. He was astonished to find that his father was not at home to receive him. The father had married again two years previously, and during the whole of the visit

Laennec's stepmother did her best to persuade him to give up medicine. Despite several letters from son to father at Sainte-Brieuc there was no sign of the latter returning home. At the end of August Laennec went to Saint-Brieuc to bring his father home. Laennec's visit lasted longer than he had expected, and he did not return to Nantes until the last week in October. He had travelled on foot from Quimper to Nantes. The journey took him over four days, and he covered an average of twenty-six miles daily.

So the years passed. As he grew older he needed more clothes, and he had often no money with which to buy them. The pathetic, and sometimes heart-rending, letters to his father continued—begging for a little money, or a few cast-off clothes. He was often threadbare and even ragged. In reply he usually received beautifully phrased advice and empty promises. Meanwhile, he lived with Guillaume and his aunt, who bore the expense. Laennec now began to wish that he could dance just a little—but that meant a dancing-master. He also developed a lasting passion for the flute. Early in 1798 he succeeded in getting some money from his father, and soon afterwards Laennec described himself as " seigneur et maître d'une belle flûte traversière." A few months later he went down with an attack of bilious remittent fever, which may, or may not, have been the beginnings of pulmonary tuberculosis.

Guillaume had of course been meanwhile impressing on Laennec that he must finish his studies in Paris. That had been obvious for some time. In the autumn of 1799 he began again the courses which he admitted he already knew by heart, and he had begun to think that he had better things to do. Early in his sixth year he became a licentiate, entitling him to practise on the local peasantry, and it was decided that he would go to Paris in the following spring.

(*To be concluded*)

FIG. 1.—René Théophile Hyacinth Laennec. (Portrait by Alexandre Dubois, 1812. The stethoscope in left foreground was added after the invention.)

(*Wellcome Historical Medical Museum.*)

FIG. 2.—Guillaume François Laennec. (Portrait by Descarsins, 1793.)

(*Wellcome Historical Medical Museum.*)

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REVIEWS OF BOOKS

Tuberculosis in White and Negro Children. Vol. 1. *The Roentgenologic Aspects of the Harriet Lane Study.* By JANET B. HARDY. Pp. 122. Illus. 60s. Vol. 2. *The Epidemiologic Aspects of the Harriet Lane Study.* By MIRIAM E. BRAILEY. Pp. 103. 36s. Harvard University Press & Oxford University Press.

These two volumes describe the experience gained at the special Tuberculosis Clinic of the Harriet Lane Home of Johns Hopkins Hospital. The clinic was established by Dr. Edwards A. Park in 1928 for the long-term study of tuberculosis in white and negro children, and new patients were accepted for inclusion in the survey until 1944. Clinical follow-up and compilation of records continued till 1950.

Volume I was written by Dr. Janet B. Hardy and is concerned mainly with the radiological aspects of the study. A brief clinical history accompanies each X-ray reproduction and the use of serial films taken over several years helps to depict the progress of the disease. A valuable chapter on bronchoscopy and bronchography in children is included.

Dr. Miriam E. Brailey is the author of Volume II which is presented in two sections. The first relates to the prognosis of primary tuberculosis in children and the second deals with the risk of developing progressive pulmonary tuberculosis.

These volumes are of merit in that they offer a number of important original contributions to the natural history of tuberculosis in childhood. Superficially, modern chemotherapy would appear to detract from the value of the research so painstakingly undertaken during the course of twenty-two years. Yet a clear concept of the epidemiology and prognosis of tuberculosis is still essential if it is borne in mind that specific remedies for this infection remain beyond the reach of more than half the population of our world.

C. W. KESSON.

Brompton Hospital Reports. Vol. 26. 1957. London: Lloyd-Luke (Medical) Books Ltd. Pp. 308. 15s. Illus.

The *Brompton Hospital Reports*, Vol. 26, for 1957, maintain the usual high standard. The Tudor Edwards Memorial Lecture by Sir Geoffrey Marshall appears in print for the first time and is a charming tribute to a great pioneer in thoracic surgery.

A new feature of this issue is the attention paid to the surgery of the heart, for it is the thoracic surgeon, through his successful intervention in cardiac disease, who has been responsible for cardiologists and specialists in pulmonary diseases coming to recognise each other's existence. The contributions by Sir Russell Brock and his colleagues on aortic stenosis form an important landmark in the further development of cardiac surgery.

In addition to the varied contributions on respiratory tuberculosis there are studies on sarcoidosis involving the bronchi; the œsophagus; fungus diseases of the lung; and respiratory granulomatosis with polyarteritis nodosa, all of which merit the closest attention.

The book is beautifully illustrated throughout and well produced. It is a pleasure to peruse its pages.

Neoplastic Disease at Various Sites. Vol. 1. *Carcinoma of the Lung.* Edited by J. R. BIGNALL. General Editor, D. W. SMITHERS. Edinburgh: E. & S. Livingstone Ltd. Pp. 298. Illus. 55s.

This is an expert treatise on " Carcinoma of the Lung," and Dr. Bignall is to be congratulated on assembling an authoritative team to deal with the various aspects of the subject. The contributions are admirably balanced and of enormous value to those interested in the subject of intrathoracic cancer, now a major problem facing workers in diseases of the chest.

The section dealing with mortality from cancer of the lung in England and Wales and a comparison with figures from selected countries is highly informative. The causation of this disease, critically reviewed by Richard Doll, and the role played by cigarette smoking, industrial fumes, atmospheric pollution, pulmonary scarring, respiratory infection, radio-activity and heredity are all weighed and considered. The conclusion is inescapable that in the absence of smoking the mortality from lung cancer in men would be reduced to between one-tenth and one-fifth of the present figure only, and in women to about a half.

Professor Smithers, in a general introduction, states that the general scheme is to discuss what is known of the factors leading to the development of neoplasia, and the possibilities of prevention or postponement which arise therefrom. It is unfortunate that there is no discussion in a work of this kind of possible preventive measures.

The pathology of carcinoma of the lung by Dr. Hinson is beautifully illustrated and provides a store of valuable information to the clinician. The laboratory procedures in the examination of bronchoscopic biopsy material, sputum and pleural effusions are lucidly explained.

Dr. Bignall's contribution is of absorbing interest, discussing the course of lung cancer from the points of view of method of investigation, site of the tumour, the effect of histological type, age and sex, situation and the length of illness before diagnosis, and unusual manifestations.

Treatment of this disease by surgical methods, radiotherapy and chemotherapy is well covered by Mr. Cleland, Professor Smithers and Drs. Galton and Papac.

The information provided here is up-to-date, clearly expressed and well presented, and the monograph has achieved its aim and purpose of being detailed and comprehensive.

It is a little unfortunate that in a work of this kind a few irritating printer's errors should have crept in.

PHILIP ELLMAN.

Le Médiastin et sa Pathologie. By M. BARIÉTY and C. COURY. Paris: Masson et Cie. Pp. 854. 312 illustrations. Fr.11,000.

Here is a reference textbook in the grand manner; vast, complete, authoritative. The work is divided into six sections. Two describe the development, structure and function, and the clinical and radiological examination of the mediastinum carefully and at length. English readers will be particularly interested in the authors' account of their use of artificial pneumo-mediastinum to define the limits and attachments of mediastinal tumors. Two sections describe the diseases caused by glandular and non-glandular mediastinal tumours, and two describe the differential diagnosis of mediastinal tumours, the changes in the mediastinum following disease of neighbouring organs, and diseases of the mediastinal pleura and mediastinal tissue. There are more than

three thousand references divided according to subject and author, British and American authors being well represented.

The writing is economical of words. Each disease is completely described: historical introduction, a definition, an estimate of frequency, pathology and classification, clinical symptoms and signs, radiological findings, special investigations, natural history and complications and treatment. Many tables summarise the opinion of authors quoted. The diagrams are clear, the photographs of diseased tissue excellent, and the many reproductions of radiographs good and to the point.

This book is a major work of reference and a fine example of French scholarship. It has the beautiful binding and presentation which it deserves.

L. H. CAPEL.

Le Pneumothorax Spontane non Tuberculeux de l'Adulte et son Traitement. By ANDRÉ MEYER, J. P. NICO and J. CARRAUD. Paris: Masson et Cie. Pp. 144. Illus. Fr.1,950.

This monograph is an interesting and up-to-date survey of various aspects of non-tuberculous spontaneous pneumothorax.

The historical section stresses the contributions of Devilliers (1826), Galliard (1888) and Kjaergaard (1932), but references throughout include many other authors, both in and outside France. There are ample sections on ætiology and pathology and the various clinical aspects of the disease are very fully discussed. In treatment, the various conservative and surgical measures are described; the authors favouring thoracoscopy with talc insufflation in recurrences.

They recommend that the air should not be withdrawn from the pneumothorax for the first three or four days to allow the fistula enough time to heal over, and that patients with even very small pneumothoraces should remain in bed for at least one or two weeks. Most authors in this country do not seem to have found those periods so necessary.

Surgical measures are recommended only when the lung fails to re-expand after prolonged aspirations or suction, as with multiple pleural symphyses, persistent broncho-pleural fistula or when the pleura is grossly thickened. The monograph does not present any new facts and the views of the authors on most subjects correspond with those widely held in this country. Surprisingly, there is no mention of honeycomb disease of the lung. The style is limpid and very readable, but at times the discussion is on rather an elementary plane. The reproductions of radiographs and illustrations are clear, these being taken from a series of sixty-five cases which the authors have studied.

ARNOLD PINES.

"*Die Dystrophie*"—*Spätfolgen und Dauerschäden.* By Dr. E. GOETZ. Stuttgart: George Thieme. Pp. 202. DM. 19.60.

This symposium describes and analyses the late sequelæ of famine as experienced by so many German soldiers and civilians during prolonged imprisonment in the last war. The syndrome which results from starvation has been termed the " Dystrophie " by the Germans. The book consists partly of a selection of papers on this subject read at a Congress. The interesting fact which emerges from these papers is that in spite of severe famine œdema, which involves almost every organ in the body, the pathological changes are

only temporary and therefore only a few of the survivors ultimately show permanent disabilities. The whole picture, however, is further complicated by the frequent coincidence of infections such as dysentery, hepatitis, tuberculosis, etc. Psychosomatic symptoms resulting from difficulties in readjustment and rehabilitation after return from imprisonment are, moreover, not rare. Nevertheless, liver damage, osteoporosis (especially of the spine) and endocarditis are sometimes the direct outcome of this syndrome.

The observations with regard to pulmonary tuberculosis are interesting. The disease occurred frequently because of the appalling conditions in the prison camps and the low resistance of the inmates. It was, however, nearly always due to reinfection rather than an exacerbation of old lesions. Many died during imprisonment. In the survivors the disease takes its normal chronic fibrotic course and the prognosis is therefore good. Reactivation of quiescent disease, when seen, was the result of typhoid fever, influenza, or following vaccination. In the young, however, a temporary deterioration of the disease was observed which occurred, not at the height of starvation, but during the actual stage of recovery.

This book can be recommended to all those interested in nutritional disease, as it gives a very good account of the vast and unfortunate experience of the Germans in famine and its late sequelæ.

H. C. NOHL.

BOOKS RECEIVED

The following books have been received and reviews of some of them will appear in subsequent issues.

A Time of Change. NAPT. Annual Report, 1957-8. London: NAPT. Pp. 48.

A Practice of Thoracic Surgery. 2nd ed. By A. L. d'Abreu. London: Edward Arnold. Pp. 619. Illus. £5.

Annual Report of City Medical Officer of Health, Durban, 1957. Published by the City Health Dept., Durban.

Glasgow's X-ray Campaign against Tuberculosis, 11th March–12th April. Glasgow Corporation Printing and Stationery Dept. Pp. 117. Illus.

Handbook of Respiration. Compiled by P. L. Altman, J. F. Gibson and C. C. Wang. National Academy of Sciences, National Research Council. Philadelphia: W. B. Saunders Company. Pp. 401. 52s. 6d.

Principles of Administration applied to Nursing Service. By H. A. Goddard. Geneva: W.H.O. Monograph Series No. 41. Pp. 108. $1.

Les Hémoptysies Tracheo-Bronchiques. By André Meyer and Jacques Chrétien. Paris: Masson et Cie. Pp. 158. Illus. F.2000.

Douzième Congrès National de la Tuberculose, Montepelier. Paris: Masson et Cie. Pp. 206. Illus. F.2,500.

Roentgenanalyse der Neugeborenen- und Saeurgerierlunge. By Zoltan Zseboek. Stuttgart: Georg Thieme. Pp. 160. Illus. DM.75.

Die Entwicklung der Tuberkulosebehandlung seit 100 Jahren. By G. Domagk. Stuttgart: Georg Thieme. Pp. 47. DM.12.

Neue Tuberkulosestatica und Tuberkulosestatica-Resistenz vin Tuberkulosebakterien. Ed. A. M. Walter. Stuttgart: Georg Thieme. Pp. 152. DM.19.80.

Grundriss der Perkussion und Askultation. By Prof.Dr.med. G. Landes and Prof.Dr. Dr. Bodechtel. Berlin: Walter de Gruyter and Co. Pp. 131. DM.9.80.

REPORTS

REPORT OF THE MINISTRY OF HEALTH FOR THE YEAR 1957

PART II—ON THE STATE OF THE PUBLIC HEALTH

SIR JOHN CHARLES in his Annual Report of the Ministry of Health for the year 1957, has some interesting observations to make concerning *clean air administration.*

The stimulus provided by the Committee on Air Pollution, under the chairmanship of Sir Hugh Beaver, whose final report led to the Clean Air Act, 1956, has not lost its force. As specifically provided for by the Act, the Clean Air Council has been established with the task of securing effective consultations between the Government and the various interests on whose co-operation the success of the clean air policy will depend. Two meetings of the Council were held during the year; and a special research sub-committee was appointed in September, 1957, " to consider the field of research and development in connection with air pollution and to indicate those subjects which, in the opinion of the committee, are of the greatest urgency or importance."

Already, 15 Smoke Control Areas have been confirmed by the Minister of Housing and Local Government, in four county boroughs, two municipal boroughs, two metropolitan boroughs and one urban district. In addition, 17 orders have been submitted, but are not yet confirmed, while 56 further proposals have been notified. It is thus plain that the problem of atmospheric pollution is now being approached with a degree of determination not hitherto encountered, despite the continual advocacy of the former National Smoke Abatement Society, now the National Society for Clean Air. Public health departments, more particularly in urban and industrial areas, may therefore regard the prevention of air-pollution as a task of high priority, demanding close co-operation between medical officers of health, public health inspectors and the alkali inspectorate of the Ministry of Housing and Local Government.

Although the need for the protection of health, life and property against polluted air should require no further argument, much research still remains to be done by engineers, scientists and health officers; indeed, this must be considered as important as the administrative and technical developments now taking place. The responsibility for such investigation rests on a diversity of official bodies and organisations, for while the first step is to deal with such " visible pollution " as smoke, grit and dust, the even more harmful gaseous pollutants present a problem which will tax the resources of all engaged in the present campaign. In so far as health departments are concerned, much contribution can be made, for example, by organising studies, in co-operation perhaps with university departments, on the relation between recorded measurements of air-pollution and the incidence of chronic bronchitis, acute respiratory infections and lung cancer. A more long-term type of enquiry would be the undertaking of detailed surveys into the health of those living in smoke control areas. But, as in the case of many other problems of environmental hygiene, the task is multiple and cannot proceed in isolation. At all times there must be effective team-work and co-operation between local authorities, the various government departments concerned, university scientific and medical workers and the medical research council itself.

Deaths associated with Fog

A dense fog in the lower Thames valley, during the period December 2-5, 1957, resulted in an abrupt increase in mortality in the London area. In the Administrative County of London (population 3,254,000) it is estimated that some 300 deaths were attributable to the fog and in the Greater London area (population 8,250,550) it is considered that the number of deaths resulting from it numbered at least 760 and may well have been over 1,000. These estimates exclude the 87 deaths in the Lewisham train disaster of December 4, which may be regarded as an indirect result.

The fog of December 2-5 is the fourth in Greater London during the past ten years to be associated with a heavy increase in mortality. That of November 26 to December 1, 1948, was considered to have caused some 700 to 800 deaths. The great fog of December 5-8, 1952, resulted in approximately 4,000 deaths and that of January 3-6, 1956, roughly 1,000.

During the period December 2-5, 1957, atmospheric pollution appears to have been heaviest in the eastern parts of Greater London area and it was here that the highest mortality occurred. If the weekly numbers of deaths registered in the nine towns, Barking, Chigwell, Dagenham, East Ham, Hornsey, Ilford, Leyton, Wanstead and Woodford, and West Ham, are taken, the total for the week ended November 30 is 200, while that for the week ended December 7, the week of the fog, is 283, an increase of 83. This is a higher proportionate increase than for London as a whole, for if the ratio of deaths during the week of the fog to the number in the preceding week is taken, the ratio for the nine towns is 1·42, that for the County of London is 1·16 and for Greater London, 1·20.

An important feature is that deaths began to show an upward trend on the first day of the fog, before the atmospheric pollution had reached its maximum. The numbers of deaths continued to rise until December 5, the last day of the fog, and then showed an abrupt fall. Similar early rises in mortality occurred in the fogs of December, 1952, and January, 1956. An early increase in the cases of acute illness requiring urgent admission to hospital has also been noted in each of these fogs. Recently the daily numbers of deaths in the Metropolitan Boroughs have been used in the investigation of a number of London fogs during the years 1954-56, and in a comparative study of the January, 1956, and December, 1957, fogs. As a result, the investigators have suggested that in London there is a critical level of four times the customary winter average of atmospheric pollution above which a fog will cause a marked immediate excess mortality. This observation, coupled with the increase in mortality noted on the first day of the fogs of 1952, 1956 and 1957 points to the toll which may be exacted by many fogs of shorter duration, where the numbers of deaths would be insufficient to be obvious in the mortality statistics.

Cancer of the Lung

Despite the attention which has been given to cancer of the lung it continues to pose a question of causation. The epidemiological studies which have been made in this country and in the United States of America have shown that excessive cigarette smoking is an important factor in its causation. But there is possibly something else working as a carcinogen upon the tissues of the respiratory tract either on its own account or in association with the smoking

habit. The identity of such a factor has not yet been established, neither do we know whether there is only one or whether there are several involved.

Tuberculosis

With regard to tuberculosis, the number of cases on the clinic registers on December 31, 1957, was 351,768. This is an increase of 556 on the previous year. There would thus appear to be a paradoxical situation in which as the number of new cases diagnosed to be tuberculous continues to fall, the number on the clinic registers is maintained.

New cases of tuberculosis (all forms) on clinic registers to the nearest thousand:

1953	..	..	44,000
1954	..	..	40,000
1955	..	..	35,000
1956	..	..	34,000
1957	..	..	32,000

The fall in both the notification of all forms of tuberculosis and the number of cases added to the clinic registers is a fact, however. That the number of cases on the clinic registers is maintained is probably a reflection of two factors. One is that among the formal notifications of respiratory tuberculosis there were 17,562 males of whom 7,856 were over 45 years of age. These are the cases which are being found in relatively increasing numbers as facilities are becoming more available to general practitioners through camera units in chest clinics, hospitals and static mass X-ray units, for the chest X-ray of all their patients showing any respiratory symptoms. Reference to the mass radiography returns confirms that there is a preponderance of tuberculosis among elderly males referred by general practitioners. In these patients there is a high proportion of the rather chronic type of disease which requires observation for a much longer period than the lesion which, discovered in its early stages, is more likely to respond satisfactorily to treatment.

The other factor is that there has been a growing tendency for chest physicians to treat their patients at home after a short period for observation and assessment. In a time of transition such as the present, when for many patients there has been a change from the strict institutional bed rest to domiciliary treatment, there is bound to be a period during which the tendency will be to keep patients on the clinic register and under supervision for a longer period than was previously customary. Some of the fall in bed occupancy mentioned under Institutional Accommodation reflects this tendency.

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NOTES AND NOTICES

15TH INTERNATIONAL TUBERCULOSIS CONFERENCE ISTANBUL (TURKEY)

SEPTEMBER 11-18, 1959

PROFESSOR ÉTIENNE BERNARD in the course of a foreword to the Conference states that "since 1950, the International Union against Tuberculosis has welcomed you to its International Conferences in Copenhagen, Rio, Madrid and New Delhi and now invites you, for the next Conference in 1959, to Istanbul. You already know the scientific programme of the Conference, which will include the consideration of a number of fundamental biological, clinical and medico-social problems. These will be treated in the form of panel discussions which should help to make them both lively and fruitful. The Conference will be held in a country where tuberculosis is still a major public health problem. The authorities of that country are therefore making a great effort to ensure the success of the Conference, to which they most heartily invite you."

Professor Frederick Heaf is Co-ordinator of the Technical Sub-Committee. Professor John Crofton is a member of the Conference Programme Committee. In the Scientific Sessions there will be symposia on the following (the Chairman's name is given in brackets): Chemoprophylaxis of tuberculosis—its experimental clinical and social aspects [Professor Robert Debré, France]. The problem of acid-fast atypical bacilli (ecology, pathogenicity for man, bacteriological characteristics) [Professor Daniel E. Jenkins, U.S.A.]. Present-day indications of surgical treatment of pulmonary tuberculosis [Sir Clement Price Thomas, Gt. Britain]. New anti-bacterial drugs [Professor L. Heilmeyer, Germany]. The problem of relapse in all its aspects. (Relapse after chemotherapy, surgery, collapse therapy, ambulatory treatment, and its importance from the epidemiological standpoint.) (*a*) Relapse after medical treatment [Professor M. Bariéty, France], and (*b*) Relapse after surgical treatment [Dr. R. C. Mitchell, U.S.A.]. New methods of rehabilitation of the tuberculous [Dr. K. Oppikofer, Switzerland]. Health education in the light of new methods of treatment of tuberculosis [Dr. Tevfik Gokçe, Turkey]. The role of the public health nurse and the social worker in tuberculosis control [Professor Jadwiga Szustrowa, Poland]. The rôle of B.C.G. vaccination in the different countries of the world [Professor Armand Frappier, Canada].

THE 4TH INTERNATIONAL CONGRESS ON TOMOGRAPHY

THIS Congress will be held at the Institute of Radiology, University of Genoa, under the direction of Professor Alessandro Vallebona, in September 1959.

The General Secretary of the Congress is Professor Neopolo Macarini, Instituto di Radiologia dell'Universita-Ospedale San Martino, Genoa.

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THE TRAINING OF THE GREATEST OF CHEST PHYSICIANS: LAENNEC

By E. Ashworth Underwood

Director of the Wellcome Historical Medical Museum and Library

Part II: Paris

At the beginning of the nineteenth century the Paris school was rapidly approaching the period of greatness which it was to enjoy for several decades. The reputation of French surgery had been greatly enhanced by the work of Pierre Desault (1744-95), surgeon-in-chief at the Hôtel-Dieu, an excellent teacher. Among the physicians Philip Pinel (1745-1826) and Jean Nicolas Corvisart (1755-1821) were outstanding. The two great protagonists of a slightly later period had not yet entered the lists: Broussais, after an adventurous early career in the army, was still a student, and P. C. A. Louis was still at school. No marked improvement had yet been effected in the great Paris hospitals. Twelve years before the end of the eighteenth century Tenon had published an important series of memoirs in which he exposed the filthy and insanitary condition of most of these hospitals. The same conditions were found in most other countries. In 1798 Pinel had inaugurated a revolution in the treatment of the insane by striking off the shackles of his mental patients at the Bicêtre, but it was years before better conditions were made available for the ordinary hospital patients of Paris.

It was into this new world that Laennec came in the last days of April 1801. In many great university cities there was a School of Medicine and several teaching hospitals, and the student had to register in both the school and a hospital. In Paris the School of Medicine was then called l'École Spéciale de Santé, and on May 2, 1801, Laennec registered for the courses in medical physics, hygiene, materia medica and internal pathology. R. N. D. Desgenettes (1762-1837), a distinguished army surgeon and hygienist, had been appointed to the chair of medical physics and hygiene by the Directory, but until after the final downfall of Napoleon he was only rarely at the École. The course was therefore conducted by Jean Noël Hallé (1754-1822), an able man who already held the title of professor in the University, and who later succeeded Corvisart in the chair of medicine at the Collège de France. Materia medica was taught by the professor of that subject, Bernard Peyrilhe (1735-1804), who in his early career was known for his work on cancer; he later turned to botany and to materia medica.

The three great teaching hospitals in Paris at that time were the Hôtel-Dieu, the Salpêtrière and the Charité. At the last-named the chief physician was Pinel, who was in the forefront of the movement for natural nosology. His book *Nosographie philosophique* (1789) went through many editions. In this work Pinel carried still further the artificial and very complex classifications

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of diseases which had been successively formulated by Boissier de Sauvages, Linnæus, Cullen and Brown. Laennec had Pinel as his professor of internal pathology at the École, and for his clinical work he chose Corvisart's clinic at the Charité. Corvisart was then approaching the beginning of his fame. He had been physician to the Charité for thirteen years, and a professor at the Collège de France for six. Three years later he was to become Napoleon's greatly respected First Physician. Corvisart was a staunch adherent of the "clinical science" practised by the ancient Greeks; and to the description of the symptoms he added that of the physical signs and a consideration of the anatomical lesions. He thus founded the Anatomico-Clinical School, and exemplified it brilliantly in his translation of, and commentary on, Auenbrugger's classic work on the art of percussion, and in his own treatise on diseases of the heart (1806). Laennec was also a close follower of the work of Bichat, who was then, at the age of 31, a pillar of the Hôtel-Dieu. He had already founded the science of pathology as based on the tissues, and he still had much work to do before his early death in 1802. There is, however, no evidence that Laennec ever attended Bichat's official courses.

During his first month in Paris Laennec took the private course of Alexis Boyer (1757-1833), the famous surgeon who did much for the teaching of anatomy in Paris. But Laennec could not afford more than one month of this course, and thereafter he had his lectures at the École de Santé and his clinical instruction at the Charité. It is certain that at the beginning he did not like Corvisart; and it is probable that, despite their daily work in the wards, Corvisart scarcely knew Laennec. Nevertheless, Laennec was very greatly impressed by Corvisart's attitude to pathology and clinical medicine. It is probable that he came more in contact with Corvisart's assistant at the Charité, Jean Jacques Leroux (des Tillets) (1749-1832), who was at that time professor of therapeutics in the École de Santé.

On his arrival in Paris Laennec intended to stay there only about fifteen months. He would present his thesis and get his degree as soon as possible, and then seek his fortune in the provinces. He therefore started to make original notes and observations at once, and among these were notes on cases of peritonitis, then a disease which was nearly always confused with enteritis. On March 24, 1802, a patient with cardiac disease, in whom Laennec had been interested, died and Laennec wrote up the post-mortem results and clinical record. He found ossification of the mitral valve and dilatation of the right ventricle. He showed his paper to Leroux, and the latter altered it and published it under Laennec's name in the *Journal de Médecine*, without giving him the opportunity to revise it or even to correct the proofs.

There was in Paris at that time another school, *l'École pratique*, which offered courses in practical dissection, operative surgery, practical pathology and practical chemistry. Since he intended to get his degree as soon as possible, Laennec did not think it was worth his while to enrol at this school. But at a later date he was persuaded to postpone the submission of his thesis for another year and to enrol at the *École pratique*. This he did in the middle of September 1802, and he therefore came into much closer contact with Gaspard Laurent

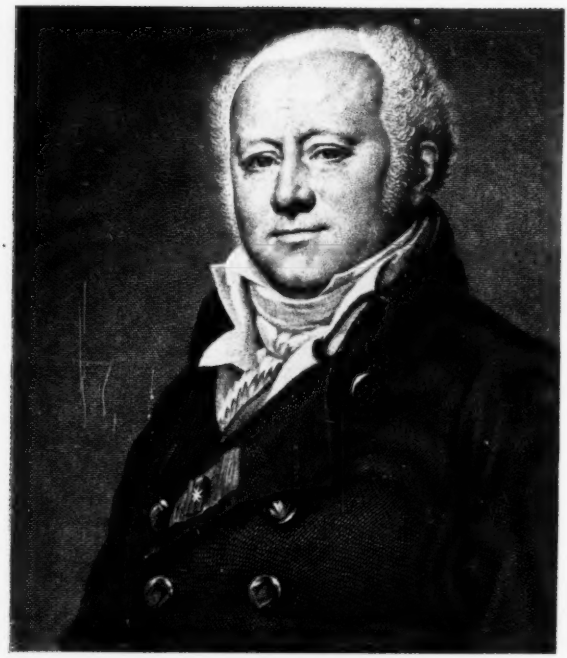

FIG. 1.—J. N. Corvisart. *By courtesy of the Wellcome Historical Medical Museum.*

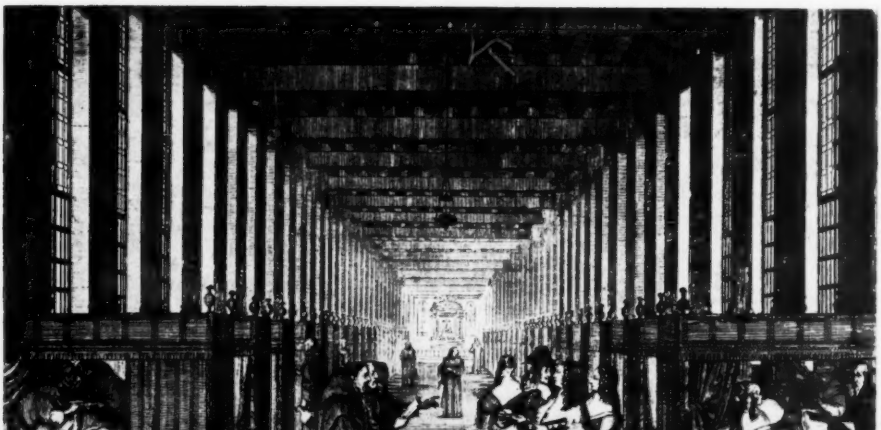

FIG. 2.—La Charité, Paris. Interior view of the wards in the seventeenth century. Line engraving by Abraham Bosse. *By courtesy of the Wellcome Historical Medical Museum.*

To face p. 123

Bayle (1774-1816), who, like Laennec later, made very important contributions to the study of tuberculosis.

In Laennec's first year at Paris the *Société d'instruction médicale* was founded. This, in contradistinction to the better known *Société d'Emulation*, was a students' society. Though founded at the Charité, it included among its members some of the best students from other schools. Laennec was a founder member. It was about this time that some of the students, of whom Laennec was probably one, desired to start a revision class in anatomy. They needed a man with some experience to attend and guide them, so they asked Guillaume Dupuytren (1777-1835), who was then in charge of practical anatomy, to recommend one of his prosectors. Dupuytren was then a young man but he was already showing something of the domineering character which later marked " le baron Dupuytren," the greatest French surgeon of his age. Contrary to expectation Dupuytren took on this small job himself, and he consequently came into closer association with Laennec. Out of this arose a prospective collaboration and a lasting antagonism.

By the middle of 1802 Laennec had written up his observations on peritonitis for publication. Forearmed by his previous experience, he did not let Leroux see the paper until it was ready to go to the printer. Leroux liked it so much that he thought that it should go out under his own name and that of Corvisart, who knew nothing whatever about it, and that Laennec's name should be tagged on merely as " rédacteur." Laennec objected strongly. After much discussion he agreed that, though his name would appear as that of the author, the phrase " Histoires recueillies sous les yeux de [Corvisart et Leroux] " should be added, since it was in their hospital that the observations had been made. This was accordingly done, and Laennec's paper was a notable contribution to pathology and clinical medicine. During the next year or so Laennec contributed several papers to the *Journal de Médecine*, including papers on the arachnoid membrane, the subdeltoid bursa (which he appears to have been the first to describe), and on the membranous capsules of the internal organs and their prolongations along the vessels. He had originally intended to present this research on the capsules as his thesis.

At that time the new subject of pathological anatomy was in the air, and Dupuytren was active in making new observations and especially in devising a new classification. He was giving a course of lectures on this subject, and in August 1802 he announced the forthcoming publication of a *Traité d'anatomie pathologique*. A few months later he added the names of Laennec and Bayle as his collaborators. It was then generally understood that Laennec would return to the provinces after he graduated. Even in February 1803 he wrote in a letter to his father that his ambition was to become a professor in some school of medicine, and that the provinces would suit him better than Paris. (The letter ends with the usual narration of his petty debts for his daily food and clothes, and the usual appeal for money.) In the following August, however, the Government announced special examinations for four medical prizes, open to students from all the medical schools of Paris. When the results were announced Laennec shared the medicine prize with Billery, but despite the alphabetical

order Laennec's name was mentioned first. Laennec also won the prize in surgery. By that time he had a better idea of his ambitions, for in a letter to his uncle in which he mentions the fine amputation set which he had received as the surgery prize, he says that he will never do surgery unless in an emergency.

Laennec's interests now centred on pathological anatomy. Dupuytren had adopted the classification of Bichat, but Laennec felt that he could not quite do so, and he determined to write his own book on the subject. In September 1803 Dupuytren presented his own inaugural thesis and re-announced his forthcoming book—this time without any mention of his two collaborators. Laennec was furious, and he decided to start his own course on pathological anatomy. By November he was ready, and the course lasted from that month until March 1804. In the following two years he repeated the course with great success, but in 1806 he was ill and it had to be discontinued. Dupuytren was annoyed at Laennec's success, and the estrangement between the two young men developed rapidly into bitter rivalry. It should be said that Dupuytren's book on this subject was never published. Neither was that of Laennec, although drafts of parts of it exist in manuscript.

Laennec had been considering a subject for his doctoral thesis, and he had chosen an essay on the doctrines of Hippocrates. He had written a lengthy essay when he found that it would be desirable for the sake of his early promotion to get the doctorate as soon as possible. He therefore selected that part of his essay which dealt with the practice of medicine and wrote it up in definitive form. This was easily done, but the regulations required that it must be published and presented in printed form. It was quite another matter for him to obtain the money for publication from his father. One fruitless letter followed another, until at length Uncle Guillaume stepped in again and made the necessary financial arrangements. This period of Laennec's life closes with the acceptance of his thesis in 1804, and his graduation as a doctor of medicine, qualified to practise medicine everywhere in France. He had already entered the field of tuberculosis as a master—but that is another story.

The reader may reflect that Laennec had spent nine years in the study of medicine before he graduated; and that, despite the fact that for some of these youthful years he was engaged daily in the service of a military hospital in one capacity or another, when he graduated in 1804 he was a man of considerable accomplishments. He spoke and wrote Latin easily, and he had a good knowledge of Greek. He also knew English and German, and had some slight knowledge of Italian. If this note is a tribute to his energy and his genius, it is also a tribute to the determination and self-sacrifice of his uncle, Doctor Guillaume Laennec, who made these accomplishments possible.

BIBLIOGRAPHICAL NOTE

The documents on which this article is based have been published by Alfred Rouxeau in his *Laennec avant 1806* (1912) and *Laennec après 1806* (1920). It would serve no useful purpose to detail the many other works which directly or indirectly have contributed information.

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BRONCHIOLITIS

By S. Engel

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Certain peculiarities in the anatomy of bronchi and bronchioli have been described in a former paper (Engel, 1958). Bronchitis and chronic bronchitis, especially the pathogenesis of chronic bronchitis, have also been dealt with (Engel, 1958). The pathological changes in bronchiolitis remain, however, to be discussed. Catarrh or inflammation of the bronchi produce cough, but bronchiolitis is not a disease associated with cough. It may be part of widespread catarrh or inflammation in the bronchial tree or may arise in the bronchioli and be more or less confined to them. General acute bronchiolitis, a serious condition, has been observed mainly in young children. Localised bronchiolitis occurs more often but is rarely recognised as the symptoms are inconspicuous or overshadowed by the signs of concomitant bronchitis.

The literature refers mainly to the clinical aspect of bronchiolitis. Textbooks deal only briefly with it (Nelson, 1954), and still more briefly with the pathology.

Bronchiolitis, especially the localised form, is, as a rule, chiefly confined to the tubules in the posterior parts of the lower lobes. It goes without saying that the narrowness of the tubules (*ca.* 0·2 mm. to 0·8 mm.) (Fig. 1)* is bound to bear on the effect of catarrh or inflammation, whether the lumen is blocked by secretion and/or the thin wall is thickened by infiltration and/or hyperæmia. The number and distribution of the bronchioli has had little attention, but these factors have an important bearing on the clinical features. Since every acinus is supplied by an individual fully epitheliated bronchiolus, the terminal bronchiolus, the number of terminal bronchioli equals the number of acini. Remembering furthermore that the lung is composed of an abundance of acini (30,000 to 50,000), that the terminal acinus is usually the third or fourth generation of bronchioli (Figs. 2, 3), the following calculation ensues, assuming the lung to be composed of 50,000 acini and the same number of terminal bronchioli:

Third order (terminal bronchioli)	50,000
Second order	25,000
First order	12,500
Total	87,500

Surprising as the enormous number is, it is likely to be too small rather than too large. In any case a vast amount of tubules may be inflamed. Fig. 2 illustrates this abundance of bronchioli. Fig. 2 is a contact photograph of a 100 μ frontal section through the right lung of a boy, aged 4 years, who died of pneumococcal meningitis whilst suffering from lobar (unifocal) pneumonia, and Fig. 3 is a diagrammatic replica of Fig. 2 showing all the bronchioli which could be ascertained with the help of a simple magnifying lens. The

* The figure numbers in the text refer to Plates II and III.

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section runs approximately through the middle of the trachea. Diagrammatic recovery of the bronchioli was necessary because many of them are too small to be recognised in the photograph with the naked eye. A section of 100 μ thickness serves the present purpose better than a thin histological section, but even a thick section can represent only a small fraction of the abundant bronchioli. Nevertheless, it is characteristic how many bronchioli have been met with in a single section. Most bronchioli are encountered in such a way that small longitudinal and many cross-cut elements can be recognised. One place only, indicated by an arrow, shows the continuation of a bronchus into a bronchiolus and its splitting into at least four generations.

The large number of bronchioli suggests that " general bronchiolitis " cannot be considered as a regional condition. As a matter of fact, acute general bronchiolitis affects the whole body, involving especially the circulation to such a degree that the clinical picture is entirely dominated by the impaired circulation, the arteries having lost their tone.

This paper does not purport to deal with the clinical features in detail; the X-ray picture alone will be described and discussed in view of the fact that its interpretation depends on the anatomical substratum. Normal bronchioli cannot be seen in skiagrams; bronchiolitis, however, may cause a characteristic picture. As already mentioned, the bronchiolar lumen, when inflamed, may be blocked by secretion (Fig. 4) and/or the wall may be considerably thickened (Figs. 5, 5A), both changes often occurring simultaneously. A single " diseased " tubule does not leave a mark on the film; passing through the lung the ray meets many, often overcrossing, bronchioli which together produce a density causing opacities on the film. The skiagram shows widespread " mottling " that resembles miliary tuberculosis or other diffuse conditions. A single tubercle or other small induration of lung tissue would not cause opacities on the film. However, if the lung is permeated by an abundance of tubercles or other small tissue condensations, the X-ray meets a number of consecutive densities and a mark on the film results. Best known is the snow-storm skiagram of miliary tuberculosis of the lung.

Mottling as produced by bronchiolitis consists of fairly soft opacities, different in density from those of miliary tuberculosis. It is, however, a diffuse mottling which may occupy the best part of both lung fields, especially the lower parts, and is so characteristic that it is of diagnostic value.

Skiagrams of the above description have occasionally been considered to indicate miliary pneumonia, a variety of bronchopneumonia, but anatomical examination contra-indicates this diagnosis. The cut surface of the post-mortem lung appears macroscopically permeated by whitish dots or longish condensations which sometimes have the shape of ductules, especially when dividing into two branches. Pictures of this kind used to be called " bronchopneumonia." Histological examination shows that the " spots " are not due to peribronchiolar infiltration but to extravagant thickening of the bronchiolar wall (Figs. 5, 5A), a condition which has been called " mural bronchiolitis " (Engel and Newns, 1938). Mural bronchiolitis may be followed by bronchopneumonia, by peribronchiolar, endobronchiolar or pedicular spread. How-

PLATE XVII

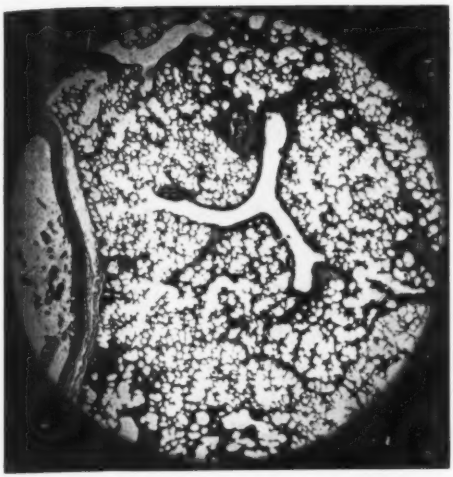

FIG. 1

FIG. 1.—Low power photograph of a lung section showing the terminal splitting of a bronchiolus and the transition into acinar tissue. ×16.

FIG. 2.—CONTACT photograph of a frontal section (100μ) lung of a boy aged 4 years.

FIG. 3.—Diagrammatic representation of the section Fig. 2. The shaded area is that of pneumonic infiltration. Bronchioli are black; the large black areas at the trachea and main bronchi are enlarged bronchial lymph nodes. Bronchi dotted, "⊙" indicates beginning of branching.

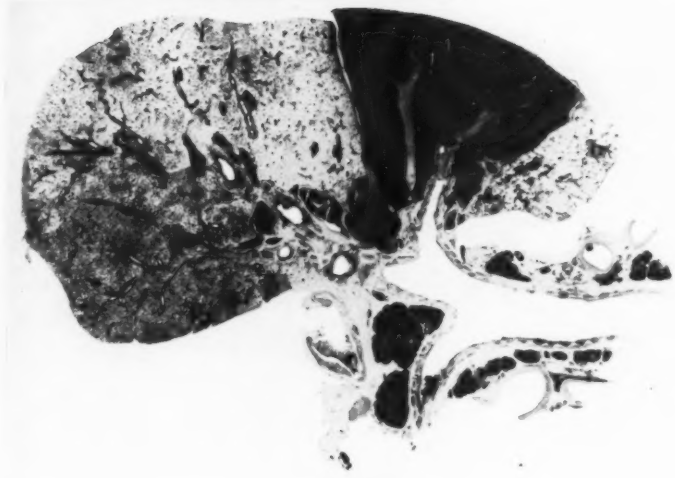

FIG. 2

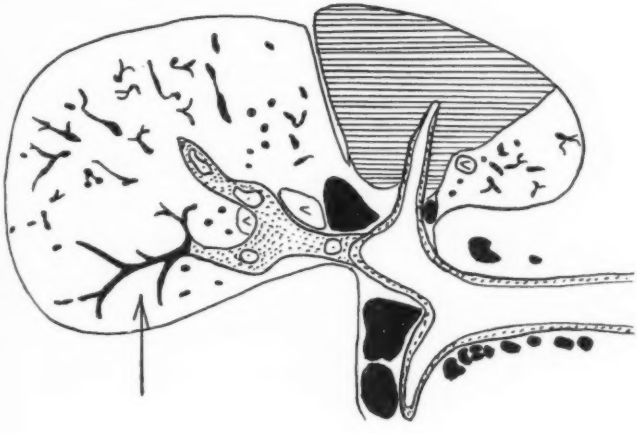

FIG. 3

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FIG. 4.—Cross cut bronchiolus, the lumen of which is filled by secretion; the wall is slightly thickened. ×33.

FIG. 5.—Typical mural bronchiolitis; the wall is greatly thickened, the lumen is free, epithelium intact. ×67.

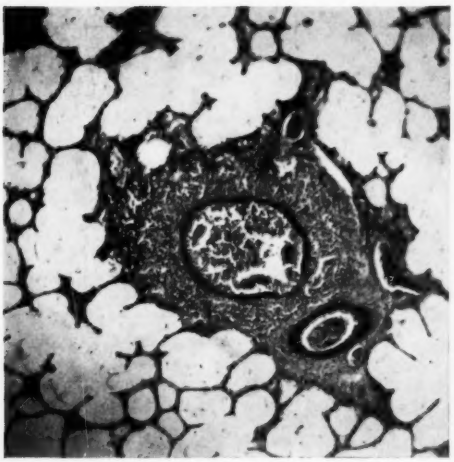

FIG. 5a.—Crosscut bronchiolus; wall enormously thickened, lumen contains secretion, epithelium partly detached. ×47.

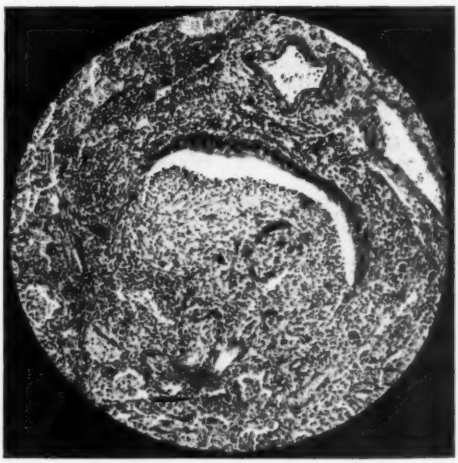

FIG. 6.—Bronchiolitis obliterans. Granulation tissue invades the lumen which is almost entirely blocked. ×67.

ever this may be, the condition begins with mural bronchiolitis, which by itself gives rise to the mottled skiagram. Mural bronchiolitis often occurs in fibro-cystic disease of the pancreas as part of general inflammation in the bronchial tree.

Bronchiolitis may turn into a chronic condition. What causes acute bronchiolitis to turn into " bronchiolitis obliterans " (Fig. 6) is not known, but I have often seen it in generally indurated lung tissue.

Summary

Bronchiolitis may occur as general involvement of the bronchioli causing a serious condition. This kind of bronchiolitis is rare and affects mainly very young children. Mural bronchiolitis may be primarily widespread or may be part of inflammation throughout the bronchial tree, especially in cases of fibro-cystic disease of the pancreas. Localised and sometimes obliterative bronchiolitis is, as a rule, less serious.

REFERENCES

ENGEL, S. (1958): *Brit. J. Tuberc. and Dis. Chest*, **52**, 277.
(1958): *Journ. clin. Pathol.*, **11**, 302.
ENGEL, S., and NEWNS, G. H. (1940): *Arch. Dis. Childh.*, **15**, 219.
NELSON, W. E. (1954): " Textbook of Pediatrics," 6th ed. Bronchiolitis, p. 823. New York: Saunders.

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A PSYCHOSOMATIC ASPECT OF ASTHMA

By J. A. Crocket

From the Asthma Clinic, Glasgow Northern Hospitals

Introduction

The characteristics of a psychosomatic illness have been aptly described by Halliday (1948), who sets out seven factors common to this type of illness:

"1. Emotion as a precipitating factor. Examination of patients in series shows that in a high proportion of cases the bodily process emerged, or recurred, on meeting an emotionally upsetting event.

2. Personality type. A particular type of personality tends to be associated with each particular affection.

3. Sex ratio. A marked disproportion in sex incidence is a finding in many, perhaps most, of these disorders.

4. Associations with other psychosomatic affections. Different psychosomatic affections may appear in the same individual simultaneously, but the more usual phenomenon, as revealed in their natural history, is that of the alteration or the sequence of different affections.

5. Family history. A significantly high proportion of cases give a history of the same or of an associated disorder in parents, relatives and siblings.

6. Phasic manifestation. The course of the illness tends to be phasic, with periods of crudescence, intermission and recurrence.

7. The prevalence is related to changes in the communal environment considered psychologically and socially. The incidence of a psychosomatic affection in a community rises and falls in response to the changes of social environment, that is, to changes of environment regarded in its psychological rather than its physical aspects."

Asthma fits neatly into this pattern. The frequency with which bouts may be precipitated by emotional factors is well recognised. A specific personality type has been described, especially in psycho-analytical literature, and a broad similarity of personality can be recognised in cases of asthma. Association with other psychosomatic affection is common, particularly with eczema, when the patient may sometimes be able to correlate visible changes in the eczema with feelings and incidents, and may find that his asthma and eczema are present alternately. Migraine, sinusitis and gastric or duodenal ulcer are not infrequently encountered in asthmatic patients.

In asthma phasic manifestation is common: probably it is best seen in infancy and the first half of childhood, and in adult life during so-called intrinsic asthma. In childhood the pattern is one of bouts of asthma occurring at intervals of two to six weeks, often associated with signs of respiratory catarrh, lasting from six to forty-eight hours and then subsiding; the child may be off-colour for twelve to twenty-four hours beforehand. The pattern

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is somewhat similar in the adult with intrinsic asthma, except that the phases of aggravation last much longer and there is rarely complete remission. The adult with extrinsic asthma also commonly shows phasic variation in severity.

Variation in the sex ratio and the frequency of a family history of allergic illness will be referred to later.

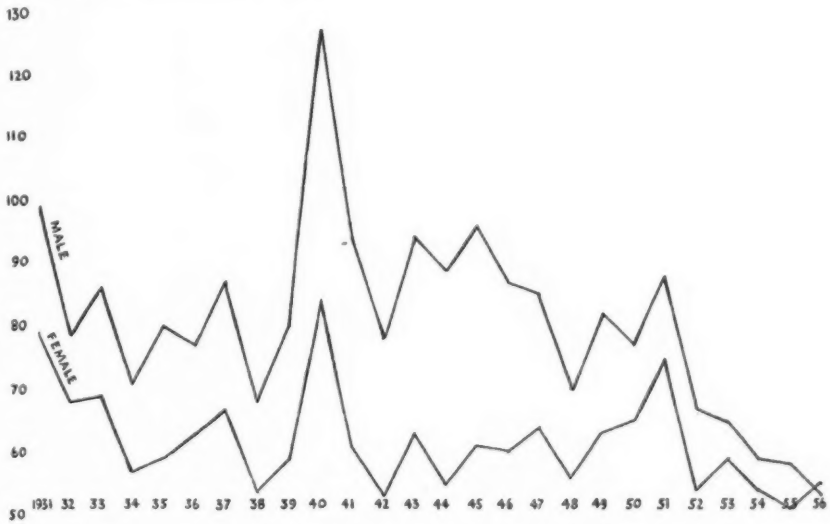

FIG. 1.—England and Wales. Deaths from asthma per million living.

It is difficult to obtain data to support or refute the relevance of the application of the seventh point to asthma, but the returns of deaths from asthma from the Registrar-General's reports give grounds for postulating an association with communal conditions. Fig. 1 gives the death rate from asthma per million living. A precipitous increase occurred in deaths following the outbreak of war in 1939. Throughout hostilities the rate for males tended to remain higher than immediately before the war years. It is difficult to explain a rise of this extent on any other grounds. The Scottish returns (Fig. 2) do not give death rates, but the records show that in this country there has been a large increase in the number of deaths since 1939. (The returns have been collected in three-year groups to smooth out the effect of year-to-year variations which in view of the small numbers might appear disproportionate.) Most of the deaths occur in people over the age of 55, but the increase has occurred at all ages and, in fact, is proportionally slightly greater in the 25- to 54-year-old group.

CLINICAL MATERIAL

1,063 cases of asthma were examined personally, and their records have been analysed with a view to assessment of the significance of psychosomatic factors.

The ages at first attendance are shown in Table 1. During the early years of the Clinic a relatively high number of children was referred, and at this period we also had a number of patients who in addition to asthma were suffering from or had recovered from tuberculosis. During the past six or seven years the main source of reference has been the general practitioner, and cases

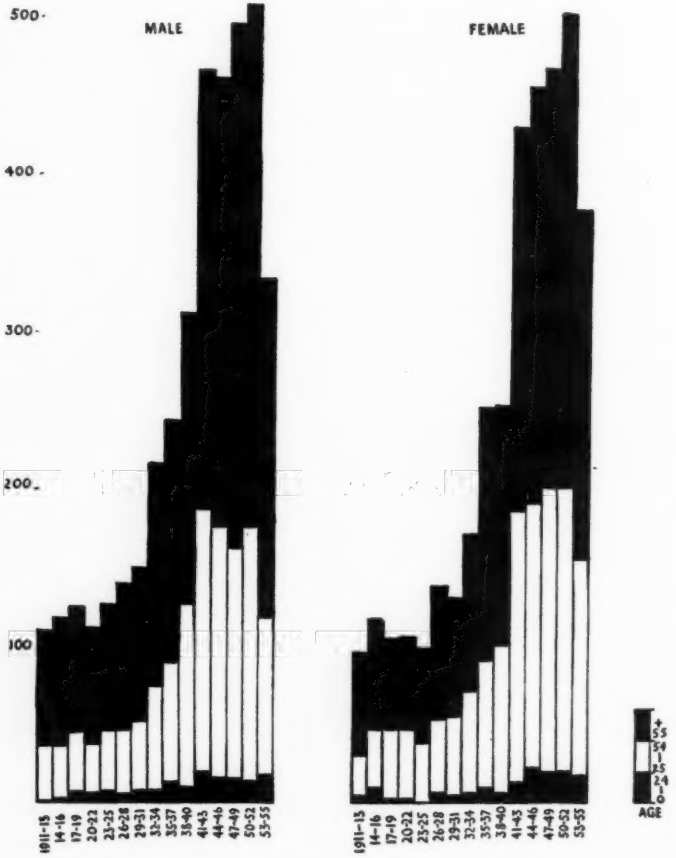

FIG. 2.—Scotland. Total deaths from asthma in three year periods 1911-55.

seen have included a higher proportion of adults. Twice as many boys as girls were referred; more women than men aged from 20 to 30 years were referred; again at 40 to 45 there was a sharp rise in the number of women seen. This table is the age at reference to the Clinic, not the age of onset of the asthma, but it is valid to assume that these peaks—for males in early childhood, and for females between 20 and 30 and 40 and 45—represent periods either of onset

TABLE 1.—AGE AT FIRST ATTENDANCE AT CLINIC

Age	MALE		FEMALE	
	Number	Per cent.	Number	Per cent.
0-5	46	9·3	26	4·6
-10	98	19·7	53	9·4
-15	84	16·9	52	9·2
-20	51	10·3	48	8·5
-25	34	6·8	63	11·1
0-25	313	63·0	242	42·8
-30	39	7·8	71	12·6
-35	33	6·6	44	7·8
-40	25	5·0	42	7·4
-45	24	4·8	61	10·8
-50	21	4·2	32	5·7
-55	14	2·8	25	4·4
26-55	156	31·2	275	48·7
-60	17	3·4	29	5·1
-65	8		13	
-70	2	2·4	4	3·4
-75	1		2	
-80	1		0	
56-80	29	5·8	48	8·5
Total	498		565	

of the asthma or of an increase in its severity or significance to the patient or his relatives. Sixty-three per cent. of males and 43 per cent. of females were under 25 at the time they were referred. One per cent. of patients were over 65 when they first came to the Clinic.

In reckoning the duration of the asthma in individual cases (Table 2) the illness has been dated from a history of two or more attacks, even when they have been followed by a period of freedom of up to several years. Many cases, of course, do not enjoy any period of freedom of significant length. Of the adult males about half are seen within ten years of the first attack, but at all ages an appreciable number come within a year of the onset of their illness. There is no significant difference in the duration of illness in female cases.

In Table 3 the decade of onset of the asthma has been calculated. Generally speaking between 65 and 70 per cent. of adults over the age of 20 develop the disease not more than ten years before their first visit to the Clinic. Surveys such as that of Williams (1951) indicate that most deaths from asthma will arise in those with intrinsic asthma, which is most frequently encountered in the group over the age of 40. The previous table, showing the age of reference to the Clinic, indicated that women were referred later in life: consequently the

age of onset is slightly later for women than for men. However, the difference is not great.

In Table 4 the age of onset in the current series is compared with the series published by Salter in 1860. Comparable figures for the first decade by Bray in his series of cases were 34 per cent. and by Unger 39 per cent. (Derbes and Englehardt, 1946).

TABLE 2.—DURATION OF ASTHMA ON FIRST ATTENDANCE

Duration of illness (years)	*Age (years)* 0-10		-20		-30		-40		-50		-60		61+		*Total*		*Per cent.*	
	M	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*
0-1	28	17	10	10	13	14	7	12	5	10	2	1	0	0	65	64		
2-5	86	47	31	39	10	44	16	25	11	22	11	15	2	5	167	197		
6-10	30	15	54	29	12	33	10	14	13	20	6	14	6	4	131	129		
-10	144	79	95	78	35	91	33	51	29	52	19	30	8	9	363	390	74	69
-20			39	22	22	36	15	21	7	21	7	8	1	4	91	112	18	20
-30					15	7	6	9	1	12	1	7	1	2	24	37	5	7
-40							4	5	4	4	1	5	1	2	10	16	2	3
-50									4	2	2	4	0	1	6	7	1	1
-60											1	0	0	0	1	0	0·2	0
61+													0	1	0	1	0	0·2
Total	144	79	134	100	72	134	58	86	45	91	31	54	11	19	495	563		

This position, in which it is shown that most cases of asthma seen at hospital developed their asthma before the age of 30, should be contrasted with the age of death—more than 60 per cent. of deaths occur in people over 56. The conclusion surely is that asthma in the young generally is not severe or permanent, but in the older patient is a very much more serious condition and should be treated as a potentially fatal ailment.

TABLE 3

Age (years)	*Number Total*	*Decade of onset of asthma* -10	-20	-30	-40	-50	-60	61+
-10	223	223						
-20	234	152	82					
-30	206	47	76	83				
-40	144	13	28	49	54			
-50	136	11	10	23	46	46		
-60	85	3	8	7	10	30	27	
60+	30	1	—	2	2	6	12	7
Total	1058	450	204	164	112	82	39	7
Per cent.		42·5	19·3	15·5	10·6	7·7	3·7	0·7

TABLE 4

Decade of onset	*Present series*		*Salter*	
	Number	*Per cent.*	*Number*	*Per cent.*
0-10	450	42	71	32
-20	204	19	30	13
-30	164	15	39	17
-40	112	11	44	20
-50	82	8	24	11
-60	39	4	12	5
61+	7	1	5	2
	1058		225	

ÆTIOLOGICAL FACTORS IN ASTHMA

On only one of the ætiological factors involved in asthma is there universal agreement, and that is the significance of a family history of allergic disease. In this series cases have been classified as having a strong family background of allergy if there is a history of allergic illness in more than two members, and a moderate background if one or two relatives give such a history. The results are shown in Table 5. About half in each age group gave a positive family history; there is no significant difference between those with a strong and moderate history. The figure of 18 per cent. in the under 10 age group is readily explained by the fact that in these children the history is derived from the parents, who naturally have a wider acquaintance with the offshoots of the family tree and their afflictions.

Cases were analysed to see whether there was any difference in social class between the sexes, with negative results. It has been suggested that the oldest and youngest members of a family are exposed to emotional stress to a greater extent than other siblings, but there was no evidence of a preponderance of children in these situations in our cases.

The main analysis of cases has been by the assessment of significance of what have been accepted as the three main factors in asthma: psychological or emotional stress; infection of the respiratory tract; and allergy. In many surveys it is assumed that these factors are mutually exclusive, and—broadly—that the younger the patient the more important the factor of allergy, while in the older patients allergy becomes of diminishing importance and infection of the respiratory tract of increasing significance. Often the psychological factor is not adequately considered.

PSYCHOLOGICAL FACTOR

To take the psychological factor first it should be remembered that until this century asthma was generally classed with the neuroses. Salter in the 1868 edition of his book says bluntly " asthma is a nervous disease." Following the various stages in the discovery of the allergic processes the psychological aspect

was relegated to the background. The current estimate of its part in asthma extends over the whole range of views, from that of the psychoanalyst to those who say that the psychological changes which can be observed in patients are the result of the asthma and not the cause.

TABLE 5.—FAMILY HISTORY OF ALLERGIC HISTORY

Family history age	*Severe*		*Moderate*		*None*		*Total*
	No.	*Per cent.*	*No.*	*Per cent.*	*No.*	*Per cent.*	
-10	38	18	70	33	102	49	210
-20	27	12	84	38	112	50	223
-30	15	8	61	32	116	60	192
-40	16	12	55	39	68	49	139
-50	14	10	45	34	75	56	134
-60	10	13	24	31	44	56	78
-61+	2	3	23	33	44	64	69
	122	12	362	35	561	53	1045

For the estimation of the strength of the psychological factor we have to depend almost entirely on the patient's story, or in the case of a child the parents', and preferably the mother's to the father's story. It is better if the story can be allowed to unfold in its own way—its pattern may be untidy but it is never illogical and the manner of its presentation may be informative. Unfortunately this needs patience and time, qualities which are scarce in clinic practice. During the earlier part of this survey, before pressure of work became severe, this procedure was adopted. Some years ago a new case sheet on a more ambitious scale was introduced with spaces for information on all conceivable points of relevance. A patient can be taken through these points more easily and quickly, but unquestionably this is done at the cost of loss of rapport with the patient and of the subtle nuances which are present if he discourses in his own way. From his story, supplemented by information of his past and his childhood, and aided by observation of the patient's reactions to steps in the investigation and his appearance, we get many disconnected items which have to be interpreted to form an assessment. These can be roughly grouped under four headings:

(*a*) Observed responses and appearances, *e.g.* overt anxiety, nail biting, response to injections, etc.
(*b*) Incidents in the history which are suggestive of an association between stress and asthma—week-end aggravation; time relationships, *e.g.* attacks of asthma in relation to stressful situations; the patient's suitability for his responsibilities and his ability to face them.
(*c*) Evidence of anxiety in childhood as shown by memories of and feelings in the parent-child relationship.
(*d*) Evidence of unconscious emotions associated with the asthma. This may

be expressed in the words used or the manner of employing expressions. The most profitable field of expression, however, is often in dreams. Not many patients admit immediately of an association, but when it is mentioned it is usually striking. The phase of aggravation of the asthma which has forced a decision to seek assistance may be associated with a period of bad dreams or nightmares. These dreams themselves may be dreams of obstruction of breathing, of being chased and unable to escape, of being strangled, and sometimes of drowning. Occasionally the pattern is one in which the patient wakens from the nightmare with asthma, the dream state of dyspnœa passing into one of conscious dyspnœa. Patients with characteristic dream patterns are often quick to appreciate the significance of this unconscious emotional factor, they welcome understanding of this aspect by the doctor, and they often respond and co-operate well in psychotherapy.

This process of assessing factors, which have been grouped under these four headings, enables one to form an opinion of the patient's personality, of his intelligence and of the degree of his neurotic anxieties. It is then possible to estimate the significance of the emotional factors in his make-up in relation to his asthma. It is not sufficient to assume that because a patient is nervous his asthma is related to his anxiety: evidence of a direct association should be sought. An appreciable number of patients are seen who have too readily been assumed to have asthma of nervous origin, when in fact their asthma is not related to their anxieties, and is of a type which responds readily to appropriate treatment.

The Infectious Factor

The assessment of the significance of the infectious factor depends on the history of and presence of infection in the upper and lower respiratory tracts. Routine chest X-rays have been taken in all patients and routine films of the nasal sinuses in all except young children. Physical examination is often more useful than radiography in assessing this factor.

The significance of signs compatible with respiratory tract infection has to be assessed somewhat differently at different ages:

(*a*) Thus, in infancy spasmodic bronchitis of a phasic character is usually non-infectious, and most commonly is allergic. The response of these conditions to early administration of antibiotics is poor; the antibiotic will clear up a secondary infection, but is without effect if given before the onset of secondary infection. On the other hand, there is a clear response to antihistamines, provided these are given in full doses, and before the condition is complicated by secondary infection.

(*b*) The phasic type of spasmodic bronchitis may continue into childhood, but generally it becomes associated with a true infective factor. Obstruction by adenoids or tonsils and mouth breathing are encountered.

(*c*) In adults the infective factor is often more important, although here also there may be a degree of allergy. The intrinsic asthma of the second half of adult life is related in some cases at least to bacterial allergy, and is often associated with thickening of the mucosa of the nasal sinuses. Frequently it

demonstrates phasic behaviour, and during the early phase of relapse sputum examination will show numerous eosinophils.

The Allergic Factor

The assessment of the allergic factor is dependent on its importance as determined from incidents in the past—such as a history of infantile eczema—from associated allergic disease such as urticaria or hay fever, and from contact with allergens, *e.g.* dust. Specific allergy is rare in infancy, and usually develops first in relation to foodstuffs of which the most frequent offenders are cow's milk, eggs, wheat, potatoes, bananas and chocolate, probably in that order. In childhood food allergy generally gives way to sensitivity to inhaled allergens of which the most significant are pollen, feathers, dust, and animal dander. Later in life mould allergy becomes more important. Skin tests are done generally by prick method in children and intradermally in adults. For the past year we have also employed inhalation tests in cases of doubt: this has been of the greatest assistance, particularly in later life and in relation to allergens such as moulds. It is evident that skin allergy varies with age, and that in the second half of adult life a slight or moderate skin reaction may be associated with marked bronchial sensitivity. In intrinsic asthma there is generally a complete absence of skin reaction or of bronchial response to inhalant allergens, but a strong response to intradermal histamine.

Correlation of Factors

The correlation of these three factors—the psychological, the infectious and the allergic—is perhaps closer than would appear at first sight. Bronchitis and sinusitis are mainly caused by infection, but there is good ground for admitting a psychological element into bronchitis, and Wolff (1953) has shown by direct observation how the nasal mucosa is affected by stress and may thereby be more prone to infection. Allergic bronchitis is a well-recognised clinical entity, and the intermittent appearance of large numbers of eosinophils in the nasal secretions and sputum during the first twenty-four hours of aggravation of chronic infection suggests that there may sometimes be an allergic process in the trigger mechanism of the relapse, particularly if eosinophils are to be regarded as carriers of antigens.

Recently Dekker and Groen (1956) have published the results of some careful experimental work on psychogenic asthma combined with an investigation into the role of allergic factors. Skin and inhalation sensitivity tests were carried out on thirty-one patients. For the inhalation tests they used a method by which the vital capacity was registered spirographically every four minutes, a decrease of 10 per cent. from the baseline being considered positive. Nine out of the thirty-one cases gave a positive result to inhaled allergens. Twelve of the thirty-one cases were also tested for the effect of psychological stimuli which were known to cause asthma in normal circumstances. Six of the twelve gave positive reactions, while four of the six who did not respond volunteered the information that the experimental condition did not resemble closely enough the circumstances under which their attacks had " naturally " occurred.

Two of the six patients who did react to psychological stimuli reacted also to inhaled allergens.

In connection with this matter of correlation of ætiological factors, reference must be made also to the summative effect of stimuli. This is commonly seen in practice, as, for instance, the individual who gets asthma when he contracts a cold, the man who had mild dog asthma, but got severe asthma when he went into a house with a dog the day before an important interview about which he was worrying. Experimentally it has been shown on the nasal mucosa of pollen-sensitive individuals how the likelihood of an attack of hay fever after the inhalation of standard quantities of pollen often depends upon whether or not there is pre-existing nasal hyperfunction in reaction to a stressful situation.

In Table 6 are listed some of the more frequent points in the history and the

TABLE 6.—ETIOLOGICAL SIGNIFICANCE OF EVENTS IN THE HISTORY

	P	*I*	*A*
Association with other illness	+	+	+
Season of onset			+
Seasonal predominance ..		+	+
Manner of onset	+	+	+
Food			+
Housing	+		+
Work	+		+
Dust sensitivity			+
Animal dander sensitivity ..			+
District	+	+	+
Weather		+	+
Weekend aggravation ..	+		(+)
Smoking	+	+	+
Menstruation	+		
Tension	+		
Feeding in infancy	+		+
Nasal symptoms	+	+	+
Skin diseases	+		+

factors to which they may contribute information of value in assessment of the significance of these factors. The list is not complete, nor is the relevance to one or more factors exclusive or encountered in every patient.

Association with other illness. There may be a history of stress illness such as duodenal ulcer, or of preceding bronchitis, or of other allergic illness such as hay fever or vasomotor rhinitis.

Season of onset. Asthma starting severely at the end of May or in June is often indicative of grass pollen allergy. If it starts in late summer or autumn the cause may be mould sensitivity.

Seasonal predominance. Summer aggravation is always suggestive of pollen or mould sensitivity. Winter aggravation may be related to bronchitis, but may be caused by a more complex allergy, for instance mould allergy and mixed dust allergy.

Manner of onset—if known to the patient—is important, and may be relevant to his condition even after a long interval. Emotional strain may be general or a specific incident. The attacks may develop out of acute bronchitis, a factor which is of particular significance in women with intrinsic asthma. An allergic onset is often more dramatic. Allergy may be occupational, as in grain handlers, bakers, wood workers and tobacco factory employees.

Food allergy is particularly important in childhood, and especially if there is a history of eczema.

Housing has to be considered from two aspects—old fabric which may be damp and harbour moulds such as *Merulius lacrymans*, the fungus of dry rot, or there may be gross overcrowding with a consequent increase in emotional tension between members of the household.

Work including school. Emotional difficulties often start at school. Usually asthmatic children are worse during school term. Many of them compensate by a good performance in the primary school, but this will not continue into secondary school unless they have the requisite intellectual capacity. One small group of children is very adversely affected, as regards their asthma, by corporal punishment, and on health grounds such punishment should be forbidden.

Dust and animal dander sensitivity are self-explanatory.

District may influence patients in all three ways. Often the aggravation which is experienced in a particular place is caused not by the place, as such, but either by the people in the house and the emotions that they stir up, or by memories—perhaps forgotten—of incidents associated with the place. Industrial districts may aggravate bronchitis. Some districts, as for instance certain wet West Coast areas, appear at times to carry very heavy pollen or mould hazards. Weather affects bronchitis and the dust, pollen and mould spore content of the air.

Week-end aggravation is common; formerly it was considered due to a change in food habits, but this is a rare cause; probably rather is it related to family feuds, resentment against religious practices, parental prohibitions, etc.

Smoking. There is a compulsive factor in heavy cigarette smoking which may have a bearing on the emotional aspect of the asthma. Cigarette smoking is often a factor in bronchitis and very often in emphysema if that is present. Rarely a true allergy to tobacco is encountered: peripheral vascular disease may be in some cases a manifestation of allergy.

Menstruation. Pre-menstrual aggravation is fairly common, but is generally mild. It may be due to general emotional disturbances, but normally is not. About one in twenty patients with pre-menstrual aggravation are affected severely, and this may be due to hyperfolliculination. The condition responds to testosterone.

Tension. Patients who have phases of tension find their bronchospasm is generally worse in these periods.

Feeding in infancy. Artificial feeding is a manifestation of maternal rejection, a state which may be relevant to the child's asthma. Weaning to cow's milk

may be associated with outbreaks of eczema, or sometimes of allergic bronchitis or asthma.

Nasal symptoms may be a manifestation of tenseness, of chronic infection or of nasal allergy.

Skin diseases—eczema, urticaria, neuro-dermatitis are often a purely allergic manifestation, but may be influenced by an emotional factor.

Information on these points has been obtained, latterly as a routine in all patients—the period at which systematic enquiry was included in the case history taking has varied with the different items. The results are shown in Table 7.

TABLE 7.—FREQUENCY PER CENTUM OF SIGNIFICANT REFERENCE TO VARIOUS SUBJECTS IN THE HISTORY

	Gastric symptoms		*Housing*		*Work*		*Dust*		*Animals*		*District*		*Weather*		*Weekend aggravation*		*Menses*	*Tension*		*Skin disease*	
Age	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*F*	*M*	*F*	*M*	*F*
0-5	15	35	29	28	9	8	13	12	11	8	13	8	4	8	24	12	—	37	35	52	35
-10	17	30	14	13	32	23	18	26	2	8	7	13	12	8	14	25	—	36	45	38	30
-20	21	28	22	22	33	36	59	48	16	17	16	14	11	12	36	31	11	31	47	35	31
-30	26	28	14	18	25	20	49	66	8	10	5	15	11	10	30	20	26	22	41	29	29
-40	40	46	13	13	33	29	67	55	12	9	16	8	16	12	31	19	31	36	58	24	23
-50	24	31	18	8	38	23	44	52	9	14	13	9	16	20	27	14	38	31	58	20	21
-60	42	46	10	—	42	17	55	48	3	11	13	20	31	33	13	9	17	48	65	13	15
61+	18	42	—	—	18	11	50	63	—	16	18	5	50	21	25	11	5	33	53	25	26
Number	121	192	84	77	149	135	221	286	46	66	59	70	68	82	123	115	118	164	284	159	148

The incidence of findings is broadly similar in males and females. Women have a rather higher incidence of gastro-intestinal symptoms, including food allergy. There is also a greater incidence of feelings of tension in women than men; this difference is only partly explicable by the relief from tension which may be obtained by work, and the impression has been gained that tension is encountered more frequently in cases with intrinsic asthma.

Week-end aggravation is greater in men than women, and generally this is due to the domestic situation from which the return to work affords relief.

THE ASSESSMENT OF MULTIPLE FACTORS IN ASTHMA

From the history and investigation on these lines it is possible to estimate the relative significance of each of the factors of psychological stress, infection of the respiratory tract and allergy. A five-point scale is used in which 1 signifies no relevance and 5 the maximum relevance. Records are available for 372 male and 447 female cases. The mean values in the two sexes in different age groups are shown in Table 8, and in Fig. 3 graphs of these values have been prepared by the method of moving averages.

The mean value for the P factor for males is 2·68, and for females 3·08. The difference of 0·4 in the two means is highly significant ($P<0.001$). A difference

TABLE 8.—VALUES OF ETIOLOGICAL FACTORS ACCORDING TO AGE AND SEX

Age range	*P Factor: average value*		*I Factor: average value*		*A Factor: average value*	
	Males	*Females*	*Males*	*Females*	*Males*	*Females*
0-5	2·36	2·00	1·81	1·77	3·19	2·77
6-10	2·71	2·97	2·24	2·35	2·97	3·03
11-20	2·46	2·93	2·37	2·29	3·18	2·89
21-30	3·00	3·10	2·25	2·20	3·46	3·11
31-40	3·06	3·29	2·20	2·35	3·38	2·88
41-50	2·61	3·24	2·47	2·76	3·19	2·98
51-60	2·62	3·04	3·13	2·61	2·63	2·91
61 and over	2·67	3·32	2·78	2·79	1·78	2·95
All ages	2·68	3·08	2·32	2·38	3·145	2·962
Standard deviation ..	1·01	0·91	0·89	0·94	0·994	0·953

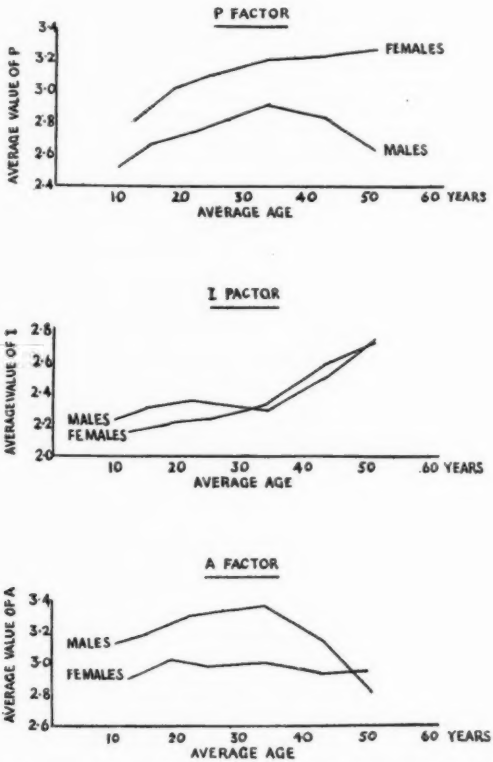

FIG. 3.—The correlation of psychological, infectious and allergic factors.

between the sexes is present at all ages, and becomes more marked in the older age groups.

The difference in the means for the two sexes for the I factor is not statistically significant. In both sexes there is a steady increase in the I factor after the age of thirty-five.

For all males the mean value of A is 3·145 and for all females it is 2·962. This difference of 0·183 in the two means is significant ($P<0.01$).

Considerable limitations are imposed on analysis of results from measurements and indices obtained largely by subjective assessments, and these findings have to be interpreted with caution. The present results suggest that the infective factor is of increasing importance after middle age, both in men and in women: it is tempting to correlate this with the increase in mortality from asthma in middle and late life. In men the association is probably with bronchitis of the ordinary chronic type, while in women the association tends to be with bronchitis associated with an intrinsic type of asthma.

The higher rates for the psychological factor in females at all ages suggest that this difference may be related to an emotional pattern which is established in early life, and is of key importance in the precipitation of asthma.

The causes of the higher figures for the allergic factor in men, and also the curves taken both by this factor and by the psychological factor in men, are less obvious. Probably the patterns are the outcome of several trends such as increased exposure to allergens at work, the higher incidence of bronchitis in men, and in later life the appearance of emphysema with increasing frequency and severity.

Summary

The relationship of ætiological factors in bronchial asthma is discussed with particular reference to the unity of the psychological and somatic aspects.

The relative importance, in a series of patients, of the psychological factor, of respiratory infection and of allergy has been shown to vary at different ages and between the sexes.

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REFERENCES

Dekker, E., and Groen, J. (1956): *J. Psychosomat. Res.*, **1**, 50.
Derbes, V. J., and Engelhardt, H. T. (1946): "Treatment of Bronchial Asthma." London.
Halliday, J. L. (1948): "Psychosocial Medicine." London.
Salter, H. H. (1860): "On Asthma." London.
Williams, D. A. (1951): *Proceedings of the First International Congress of Allergy*. Basel.
Wolff, H. G. (1953): "Stress and Disease." Springfield.

Brit. J. Dis. Chest (1959) **53**, 142.

THE BRONCHIAL SPREAD OF LUNG CANCER

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Since Evarts Graham performed the first successful pneumonectomy for primary lung cancer in 1933 (Graham and Simpson, 1933), surgery has been the recognised treatment of choice in this common form of malignant disease. Where the disease is still sufficiently localised to be operable, pneumonectomy has been considered to be the standard treatment, either as a simple dissection pneumonectomy, or the more radical pneumonectomy devised by Higginson (1953) in America and Brock in this country (Brock and Whytehead, 1955). The mortality in this operation is similar to that of a simple pneumonectomy, in most of the large series reported of the order of 10-15 per cent. Unfortunately the disability rate of the survivors is very high and many are confined to a very restricted existence as cardio-respiratory invalids.

Many of the patients presenting with carcinoma of the bronchus are elderly and are often sufferers from chronic bronchitis with emphysema and respiratory insufficiency. In such subjects pneumonectomy is a hazardous undertaking, and where the local spread of the disease process allows it, the more limited operation of lobectomy has been performed, resulting in a lower mortality rate with much less risk of producing gross respiratory insufficiency. Belcher, (1956), in a large series of lobectomies, found the survival rate to be similar to that in cases subjected to pneumonectomy, a feature also noted by Churchill, Sweet, Soutter and Scannell (1950). In recent years, the operation of lobectomy with sleeve resection of the bronchus has been performed in some surgical units with the purpose of increasing the margin of local bronchial excision in selected cases where the tumour involves, or is close to, a main lobar bronchial orifice.

On general principles the surgery of malignant disease should aim at a wide local excision of the affected tissues, together with the regional lymph nodes. Doubt has therefore been cast on the operation of lobectomy on the grounds that neither of these criteria is fulfilled.

Carcinoma of the bronchus spreads by direct invasion of neighbouring tissue, by lymphatics with lymph node invasion, and by the blood stream. The high incidence of early blood-borne metastasis is largely responsible for the overall poor survival figures in this disease and has been recently stressed by Collier, Kyle, Enterline, Tristan and Greening (1957) and by Johnson, Kirby and Blakemore (1958) as the most important factor in the prognosis. There is little, however, that the surgeon can do about this, and recognition of blood vessel invasion can usually only be found in the subsequent histological examination of the affected tissue. Nohl (1956) in a recent extensive study of the lymphatic spread of the disease has suggested that there is no contra-indication to lobectomy in selected cases in this respect. From the point of view of adequate local removal of the tumour, the direct method of spread becomes of great impor-

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tance, particularly the site of section of the bronchus, since this will be to a large extent the controlling factor in the amount of lung tissue which has to be sacrificed. Little or no attention has been paid to the pathological features of the bronchial spread, with the exception of Griess, McDonald and Clagett (1945), who found evidence of proximal spread of the tumour in one or more layers of the bronchial wall in 13 of the 30 cases examined. This direct proximal extension of the tumour was most commonly seen in the better differentiated squamous cell carcinomata, the furthest extent being 1·5 cm. This, however, is but one of the methods of extension of the tumour in relation to the bronchus, and it was considered that further information of practical value might be gained from the detailed examination of all the factors involved in the bronchial spread of lung cancer.

Materials and Methods

The material for this survey was obtained by detailed examination of 100 consecutive specimens of carcinoma of the bronchus removed surgically at the Middlesex Hospital in the years 1955-58. Post-mortem material was excluded for two reasons:

1. Autolytic changes, with gross distortion of histological appearances, occur rapidly in lung tumours and in surrounding tissues, particularly when, as is very common in this disease, infection is a notable feature.
2. When the disease is very advanced with extensive hilar and mediastinal gland invasion, the site of origin of the tumour is very difficult to determine and anatomical relationships are exceedingly difficult to assess.

The material was made up as follows:

	Cases
Right pneumonectomy	21
Right lobectomies	31
Total right	52
Left pneumonectomy	34
Left lobectomies	14
Total left	48
Total number of cases	100

The specimens were all received fresh and after preliminary examination were inflated via the cut end of the bronchus with 10 per cent. formol-saline until the normal dimensions and relations of the tissue were approximately restored. The procedure also ensured good fixation for subsequent histological examination. After 12-24 hours of preliminary fixation, the lung was incised to give a longitudinal view of the tumour in relation to its bronchus of origin. The macroscopical features of the tumour in relation to the bronchial tree were recorded, in addition to the routine dissection, charting of lymph nodes, and other features. After a further short period of fixation in formol-saline,

blocks of tissue for histological examination were taken from the tumour and adjacent bronchus. Several blocks of tissue, normally in the longitudinal plane, were taken from each specimen, care being taken to include the junctional area of tumour and apparently normal bronchus, and neighbouring bronchi. Many sections from each of these blocks of tissue were examined.

Results

There are five factors of importance in this type of spread:

1. Direct extension in continuity of the tumour.
   (*a*) In the bronchial wall.
   (*b*) In the para-bronchial tissues.
2. Involvement by direct extension of bronchi other than the bronchus of origin, particularly in relation to tumours arising close to the major lobar bronchial orifices.
3. Invasion of sub-mucosal lymphatics in the bronchial wall.
4. Extension of the tumour proximally along the lumen of the bronchus by papillary or polypoid processes without further attachment to the bronchial wall.
5. The presence of epithelial metaplasia, particularly when the epithelial change shows atypical proliferative features.

In any individual case, more than one of these may be present, but there is usually one dominant feature, as will be seen by the subsequent analysis of results.

1. *Direct extension of the tumour*

This factor is present in every case where a bronchial connection is demonstrable, both along the bronchial wall and in the para-bronchial tissues. The following results indicate the relative frequency of para-bronchial and bronchial spread, the measurements indicating the maximal proximal extent of the spread in relation to the tumour.

Para-bronchial spread	.. ..	64
0-$\frac{1}{4}$ in.	11	
$\frac{1}{4}$ in.-$\frac{1}{2}$ in. ..	35	
$\frac{1}{2}$ in.-1$\frac{1}{2}$ in. ..	18	
Spread along bronchial wall ..	..	12
0-$\frac{1}{4}$ in	4	
$\frac{1}{4}$ in-$\frac{1}{2}$ in. ..	6	
$\frac{1}{2}$ in.-$\frac{3}{4}$ in. ..	2	
Level	..	16
No demonstrable bronchial connection ..		8
Total	..	100

It will be seen from this that the parabronchial factor is much more common than extension along the bronchial wall. The tumour extends in the lung tissue alongside the bronchi, sometimes forming a cuff of tissue around the

FIG. 1.—Operation specimen showing extensive para-bronchial spread with involvement of the upper-lower lobar carina.

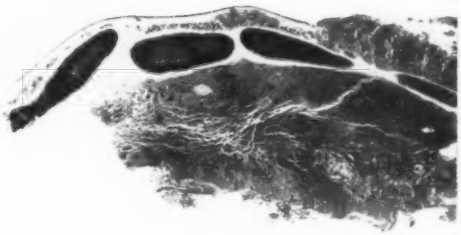

FIG. 2.—Low-power view to show para-bronchial extension. ($\times 4\frac{1}{2}$)

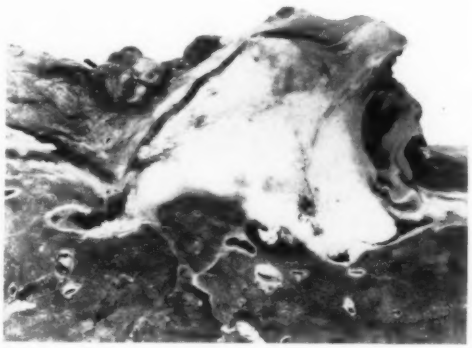

FIG. 3.—Pneumonectomy specimen showing extensive bronchial and para-bronchial spread from upper lobe to involve lower lobe and main bronchi.

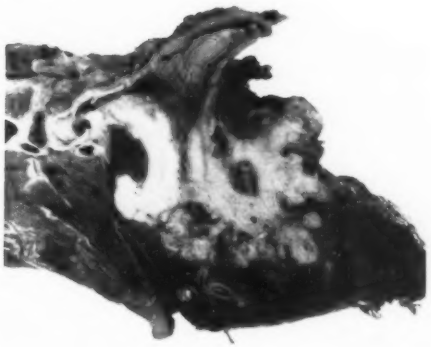

FIG. 4.—Operation specimen showing involvement of the lower lobe bronchus by a tumour arising in the upper lobe.

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wall (Figs. 1 and 2).* In 6 of these cases, columns of tumour cells re-invaded the bronchus from the para-bronchial tissues; in 2 cases this was confined to the fibrous outer coat of the bronchus, but in 4 cases columns of cells were invading between cartilaginous rings into the sub-mucosa. In none of these cases was the mucosa affected. Para-bronchial spread is recognisable by palpation and there is seldom any significant degree of microscopic extension beyond the naked-eye margin. Secondary invasion of the bronchus from the parabronchial tumour is unlikely to be of any practical significance, as this portion of the bronchus will be removed with the tumour and attempts to strip the bronchus away from the tumour are to be discouraged on this account.

In 16 cases there was no significant difference between the para-bronchial and bronchial wall extension.

The remaining 12 cases showed extension in the bronchial wall proximal to any tumour in the surrounding tissues. In 2 cases this was $\frac{5}{8}$ in. and $\frac{3}{4}$ in. respectively. In 6 instances the extension was mucosal with irregularity and thickening obvious macroscopically (Fig. 3). In the others most of the extension occurred in the sub-mucosal tissues with a covering of intact epithelium and minimal thickening of the wall (Fig. 6), not obvious to the naked eye; or in the outer fibrous coat (Fig. 5). These findings are generally in agreement with those described by Griess (1945). This would seem to indicate that there should be a margin of at least $\frac{3}{4}$ in. of apparently normal bronchus proximal to macroscopic tumour, if the risk of leaving behind tumour cells in the bronchial wall is to be eliminated.

2. *Involvement of Other Bronchi*

This occurs in two ways:

1. By invasion of the wall of other bronchi by tumour-invaded lymph nodes.
2. By direct extension of the tumour to invade neighbouring bronchi.

The first factor was only seen in two instances. On both occasions there was an enlarged tumour-invaded lymph node at the upper-lower lobe carina invading and compressing the other main bronchus. This appearance is seen with greater frequency in advanced disease where tumour-invaded intra-pulmonary and mediastinal glands may compress and invade neighbouring bronchi to produce bulging and ulceration of the main bronchi or trachea sometimes obvious at bronchoscopy.

In 3 cases there was gross extension of tumour across the major fissure to produce invasion of bronchi in the other lobe.

In 32 cases the tumour was close to or involving a major lobar orifice, thereby excluding simple lobectomy. Twenty-one of these tumours were in the upper lobe and 11 in the lower lobe. Examination of the bronchus in these cases included not only the proximal portion but also that part of the other lobar bronchus distal to the lobar carina which would be removed by a sleeve resection.

* The figure numbers in the text refer to Plates IV-VI.

Of the 32 cases where the tumour was at, or very close to, the lobar orifice, 22 showed involvement of the other lobar bronchus (Fig. 4). This distal type of spread is analysed as follows.

Para-bronchial spread	18 *cases*
0-$\frac{1}{4}$ in.	2
$\frac{1}{4}$ in.-$\frac{1}{2}$ in. ..	6
$\frac{1}{2}$ in.-1$\frac{1}{4}$ in. ..	10
In the bronchial wall	15 *cases*
0-$\frac{1}{4}$ in.	6
$\frac{1}{4}$ in.-$\frac{1}{2}$ in. ..	5
$\frac{1}{2}$ in.-$\frac{3}{4}$ in. ..	4

The greatest para-bronchial spread was 1$\frac{1}{4}$ in. and the furthest extension in the bronchial wall seen was $\frac{3}{4}$ in. Retrograde lymphatic invasion was not seen in this series nor were other tumours seen in the bronchi.

Thus, in tumours involving the main lobar bronchial orifices a high percentage cannot be resected by lobectomy. Removal of an adequate sleeve of bronchus will give a satisfactory margin of local excision in the majority of cases.

3. *Invasion of Sub-mucosal Lymphatics*

There was obvious invasion of the sub-mucosal lymphatics in 6 cases. In 2 cases this feature was noted only in the bronchial wall immediately adjacent to the tumour and was not proximal to the para-bronchial direct spread. In 4 cases there was extensive lymphatic invasion extending for a considerable distance along otherwise normal bronchus, with no hint of this phenomenon on macroscopic inspection. In 2 of these cases this feature was noted up to the limit of bronchial resection more than 1 in. proximal to the tumour. In all 6 there was extensive invasion of the intra-pulmonary and mediastinal lymph nodes. This factor in itself would suggest a very unfavourable prognosis. The presence of extensive sub-mucosal lymphatic spread is probably of grave significance as illustrated by one of these cases. Left pneumonectomy was performed for a tumour of the left lower lobe. Examination of the specimen showed over 1 in. of apparently normal bronchus proximal to the naked eye extent of the tumour, but histological examination revealed sub-mucosal lymphatic spread to the limit of resection (Fig. 7). The patient died four months later and at post-mortem was found to have widespread blood-borne metastases and a large mass of invaded glands in the right mediastinum. Examination of the region of bronchial suture and right main bronchus showed similar tumour in sub-mucosal lymphatics extending well down the wall of the right main bronchus (Fig. 8). Nohl (1956), in his account of the lymphatic spread of lung cancer, mentioned a similar case and two others exhibiting to a lesser extent this method of spread. As a result of his findings he suggested that tumours of the main bronchi between 1 and 2 cm. from the carina should be deemed inoperable because of the sub-mucosal lymphatic spread. In a study of 154 patients with bronchial carcinoma, Rabin, Selikoff and Kramer (1952), by performing

para-carinal biopsies, found evidence of proximal tumour spread in 16 per cent. which seemed to be operable on other grounds. In some of these there was sub-mucosal lymphatic invasion, the others were presumably due to direct bronchial extension such as has been noted in this series. Rabin comes to a similar conclusion to Nohl with regard to operability of tumours close to the carina. The incidence of this spread is comparatively low and should be kept in perspective with other factors, suggesting that perhaps both Nohl and Rabin over-emphasised its importance.

It is worth noting that distal retrograde lymphatic spread in other bronchi was not seen in this series, although it remains a theoretical possibility once lymphatic obstruction by tumour has occurred.

4. *Polypoid Processes*

Sixteen of these tumours exhibited a tendency to polypoid form within the bronchial lumen and to extend proximally along the lumen without further attachment to the wall. These processes may extend for a considerable distance, 1¼ in. in one case, and may occlude other segmental or lobar orifices. In some of these cases very fine blood vessels may be seen crossing from the adjacent bronchial wall to the mass within the lumen, but there is no evidence of invasion of the neighbouring bronchus (Figs. 9 and 10).

The frequency and extent of this feature is shown as follows:

	Proximal to tumour in and around bronchial wall	*Not extending beyond tumour in and around bronchial wall*
0-¼ in.	0	3
¼ in.-½ in. ..	1	4
½ in.-1¼ in. ..	7	1
Total ..	8	8

One case is of particular note in which a tumour of the right lower lobe extended through the lobar orifice by such a polypoid process 1 in. long and caused collapse of the middle lobe and partial collapse of the upper lobe by occlusion of the bronchial orifices. At no point was the bronchial wall invaded after its origin in the lower lobe. Radiological and bronchoscopic examinations before pneumonectomy had suggested the disease was advanced, whereas a more local operation could, in fact, have been performed.

There are obvious practical difficulties in recognising this type of spread when it occurs. Little evidence may be apparent from bronchoscopic or bronchographic examination and probably the only way in which it may be discovered is by opening the bronchus. This procedure is open to criticism on the grounds that the tumour may be disseminated or implanted by such a manœuvre. When preservation of lung tissue is of the greatest importance,

however, this form of polypoid extension may give an opportunity for a more local yet adequate resection.

5. *Epithelial Metaplasia*

There is by no means universal agreement among pathologists on the significance of epithelial changes in the respiratory tract, but there are certain features of note in this series which are worth recording.

Squamous metaplasia was seen in 31 of the cases in this series.

In the immediate proximity of the tumour only ..	17
Moderate proximal extension (up to ½ in.)	6
Extensive proximal extension (½-2 in.)	8
	31

All these tumours were squamous-cell carcinomata.

In one additional case of oat-cell carcinoma there was extensive atypical epithelial change similar to that described in 2 cases by Williams and Howard (1958), and called by them " *in situ* carcinoma."

The histological appearance of the squamous metaplasia varied from a quite regular squamous type of epithelium to areas of highly atypical proliferation with irregularity of cell size, mitotic figures and loss of polarity of cells. This last type of change is indistinguishable from the intra-epidermal carcinoma, seen as Bowen's disease in the skin, and must, therefore, be regarded as pre-invasive or *in situ* carcinoma. There may be a continuous zone of epithelial abnormality extending in a graded manner proximal to the tumour in the order, invasive carcinoma, pre-invasive carcinoma, atypical squamous epithelium, thickened squamous epithelium, regular squamous epithelium and, finally, normal ciliated columnar respiratory epithelium. In one case a right lower lobectomy was performed for squamous-cell carcinoma. Examination of the specimen showed a wide margin of local excision and the lymph nodes were tumour free. There was, however, squamous metaplasia extending to the limit of resection (Fig. 11). Two years later it was necessary to remove the remainder of the lung for tumour recurrence in the region of the bronchial stump. In this later specimen the graded epithelial metaplastic change extended for 2 in. along the upper and main bronchi (Fig. 12). It appears likely that the squamous epithelium left behind by the first operation had subsequently developed into a further carcinoma. Whether one regards this as a second primary tumour or a recurrence is debatable, but Habein, McDonald and Clagett (1956) have shown the importance of this factor in producing bronchial stump recurrence. Most of their 18 cases of recurrence at the stump showed extensive epithelial metaplasia to the limit of the original resection.

In this series the tumours showing the extensive areas of atypical metaplasia were mostly keratinising cell carcinomata. Such a tumour carries a much better prognosis with adequate surgical treatment than other histological types, and it would seem wiser to remove these tumours as widely as possible to avoid leaving behind potentially dangerous areas of epithelial change.

Discussion and Conclusions

From these results three factors emerge which can lead to inadequate local excision of the tumour.

1. Direct extension of the tumour in the bronchus proximal to the tumour mass—12 per cent.
2. Sub-mucosal lymphatic spread—6 per cent.
3. Epithelial metaplasia of significant extent—15 per cent.

If these factors are ignored, recurrence rates relative to the respective frequencies are to be expected.

The extent of the first factor agrees fairly closely with that found by Griess (1945), who suggested a margin of apparently normal bronchus of 1·5 cm. The results in this series suggest that if the slightly higher figure of $\frac{3}{4}$ in. is observed, all but exceptional cases of bronchial wall extension will be eliminated and this will also cover most of the instances of epithelial metaplasia.

The factor of sub-mucosal lymphatic spread, in view of the incidence of extensive mediastinal lymph node involvement, is important in that it seems doubtful, when this occurs, if any normal form of surgical resection will affect the fatal outcome.

Where tumours involve, or are close to, the main lobar bronchial orifices this margin of resection cannot be obtained by simple lobectomy, and in view of the high incidence of involvement of the other lobar bronchus it is necessary to resect a further portion. These results show that in most cases the operation of sleeve resection will provide the necessary clearance of the tumour and, if $\frac{3}{4}$ in. is allowed both proximally and distally, most if not all of the excisions will be complete. Parabronchial spread to the other lobe may extend further than this, but in doing so the fissure will be transgressed, thereby ruling out any possibility of lobectomy.

Provided that these factors are kept in mind in selecting the cases, the operations of lobectomy and lobectomy with sleeve resection have a sound pathological basis from the aspect of bronchial spread and the local recurrence rate should be negligible.

In cases where these criteria cannot be fulfilled, the chances of recurrence will undoubtedly be higher, but the relative frequency of these adverse factors should be kept in perspective and there is no real justification for deeming all such cases inoperable.

Summary

One hundred consecutive surgically resected specimens of primary lung cancer were examined in detail to determine the methods and extent of spread in relation to the bronchus.

1. Direct extension in the bronchial wall proximal to the main tumour mass occurred in 12 cases; furthest $\frac{3}{4}$ in.
2. Direct involvement of other bronchi by direct extension or tumour-invaded lymph nodes is rarely seen at a stage when the tumour is still

operable, with the exception of tumours close to, or involving, the major lobar orifices. Twenty-two out of 32 of such tumours in this series showed distal involvement of the other lobar bronchus by para-bronchial spread, furthest 1¼ in., or spread in the bronchial wall; furthest ¾ in.

3. In 6 cases there was invasion of sub-mucosal lymphatics, in 4 of these of considerable extent, the furthest more than 1 in. All these cases had extensive mediastinal lymph node invasion.
4. Extension of the tumour along the bronchial lumen by polypoid processes without further attachment to the wall was seen on sixteen occasions. In 8 of these cases this was the most proximal means of spread and measured in seven instances between ½ in. and 1¼ in.
5. Thirty-two cases showed epithelial metaplasia in the bronchus proximal to the tumour; in all but one, this was of a squamous nature. In 17 cases this was confined to the immediate proximity of the tumour, in the remaining 15 the distance varied from ¼ in. to 2 in.

The practical implications of these findings are discussed in relation to the surgery of lung cancer.

If these factors are kept in mind and certain criteria adhered to, there is no contra-indication to lobectomy from the bronchial spread aspect.

Where the tumour is close to the major lobar orifices, sleeve resection of the other bronchus should be performed when a pneumonectomy is contra-indicated.

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REFERENCES

Belcher, J. R. (1956): *Lancet*, **i**, 349.
Brock, R., and Whytehead, L. L. (1955): *Brit. J. Surg.*, **43**, 8.
Churchill, E. D., Sweet, R. H., Soutter, L., and Scannell, J. G. (1950): *J. thorac. Surg.*, **20**, 349.
Collier, F. C. D., Kyle, R. H., Enterline, H. T., Tristan, T., and Greening, R. (1957): *Amer. J. Path.*, **33**, 582.
Graham, E. A., and Singer, J. J. (1933): *J. Amer. med. Ass.*, **101**, 1371.
Griess, D. F., McDonald, J. R., and Clagett, O. T. (1945): *J. thorac. Surg.*, **14**, 362.
Habein, H. C., McDonald, J. R., and Clagett, O. T. (1956): *J. thorac. Surg.*, **31**, 703.
Higginson, J. F. (1953): *J. thorac. Surg.*, **25**, 582.
Johnson, J., Kirby, C. K., and Blakemore, W. S. (1958): *J. thorac. Surg.*, **36**, 309.
Nohl, H. C. (1956): *Thorax*, **11**, 172.
Rabin, C. B., Selikoff, I. J., and Kramer, R. (1952): *Arch. Surg., Chicago*, **65**, 822.
Williams, M. J., and Howard, S. A. (1958): *Cancer*, **11**, 939.

Brit. J. Dis. Chest (1959) **53**, 151.

CHEST DEFORMITIES IN CONGENITAL HEART DISEASE

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Introduction

Some children with congenital heart disease have chests of unusual shape. Hitherto no attempt seems to have been made to relate these changes to the underlying pathology. The present study was undertaken with this in mind, and was initiated by some clinical observations on children with septal defects.

The first patient was a child of seven who had recently undergone surgery for closure of a ventricular septal defect, using cardiac bypass and a pump oxygenator. He was extremely dyspnœic, and the small chest appeared blown-up and barrel-shaped. The sternum jutted forward and was lifted laboriously with each breath; at the same time the lower ribs were sucked in during inspiration. The picture was at once reminiscent of the severe respiratory embarrassment of an asthmatic attack, or of the exacerbations of illness in patients with chronic bronchitis and emphysema.

It became apparent that this respiratory distress was much more common in children with ventricular septal defects (V.S.D.) than in those with atrial septal defects (A.S.D.) at a corresponding post-operative stage, and that this could not be accounted for entirely by the diminished trauma and metabolic upset occasioned by the techniques of hypothermia as compared with the artificial circulation. When it was observed that children with V.S.D. had, by and large, a different chest shape from those with A.S.D., the question arose as to whether or not there was any relation between the chest deformity and the nature of the cardiac lesion, and, if so, whether any significance could be attached to this in view of the manifest differences in behaviour of the two conditions.

The contour of the chest in the sagittal plane is fairly accurately represented in the lateral chest X-ray, and it is on this basis that the study has been carried out. Before describing the methods and results, the clinical features of the chest deformities will be described. In patients with an A.S.D. a chest deformity is present in about one-half of the cases (Taussig, 1947; Swan *et al.*, 1959). This deformity consists of a protuberance in the region to the left of the lower sternum where the pulsation of the right ventricle is felt. The upper sternal region is usually normal or flat and tends to be narrow in the antero-posterior diameter, the bulge being low and unilateral (Fig. 4).* In the V.S.D., on the other hand, the sternum itself appears to bulge high in its contour, the lower regions being rather indrawn. Furthermore, the prominence is usually bilateral. Sometimes

* The figure numbers in the text refer to Plates VII and VIII.

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the angle between manubrium and sternum is sharp; sometimes the convexity forward assumes the form of an arc embracing the whole of the anterior chest from supra-sternal notch to ziphisternum. These differences are recognisable clinically without great difficulty.

Material and Methods

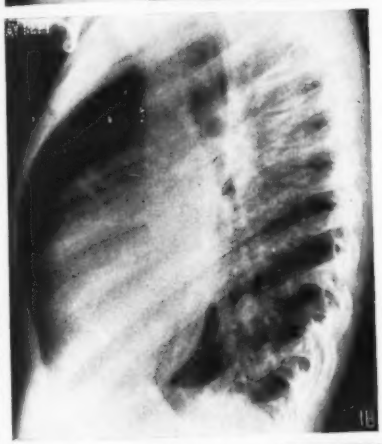
The chest X-rays of 100 cases of A.S.D. and approximately 100 of V.S.D. have been examined. All these patients had undergone cardiac catheterisation. Only those in whom an adequate lateral X-ray was available have been retained in the study, as obliquity distorts the sternal contour. When this criterion had been satisfied, there remained 80 cases of A.S.D. and 45 of V.S.D. The former ranged in age between 1 year and 45 years, whilst all the latter were between 3 and 14 years of age except case 45, who was 24 years old. An attempt was made at first to record accurately, in terms of angles and ratios, the mensural characteristics of the X-rays, but this was found to be unrewarding, owing to the variations in shape, posture and size. Accordingly, the degree of upper sternal prominence has been graded " blind " (*i.e.* without knowledge at the time of the diagnosis or the hæmodynamic findings) into " severe," " moderate " or " absent". Those cases in whom the deformity was thought to be only mild have been included in the latter group. It is emphasised that the deformity sought has been that of the " V.S.D. type " described above. Examples of the X-ray appearances are shown in Fig. 1 (severe) and Fig. 2 (moderate deformity). Fig. 3 shows, for contrast, a normal lateral X-ray of a patient with V.S.D. (case 28), and Fig. 4 that of a case of A.S.D., showing that the lower sternal contour appears bifid on account of the unilateral protuberance.

Results

Severe upper sternal deformity (V.S.D. type) (Fig. 1) was present in 11 of the 45 cases of V.S.D. and in none of the A.S.D. cases. Moderate deformity was seen (Fig. 2) in a further 11 cases of V.S.D., and again in none of the A.S.D. cases. Thus, the deformity was seen in 22 of the cases of V.S.D. as compared with none in A.S.D. The results are summarised in Table I.

Table 1.—Incidence of " V.S.D.-type " Deformity in 45 Cases of V.S.D. and 80 of A.S.D.

	V.S.D.	*A.S.D.*
	Cases	*Cases*
Severe deformity	11	0
Moderate deformity	11	0
No deformity	23	80
	45	80



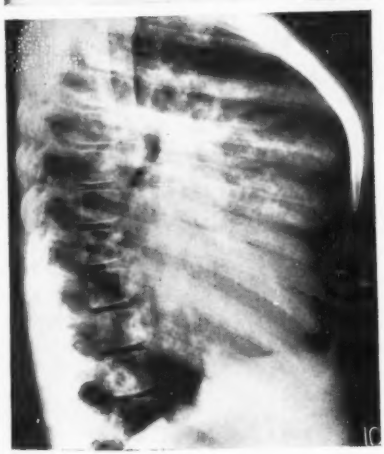


FIG. 1.—Three cases of severe chest deformity (V.S.D. type).

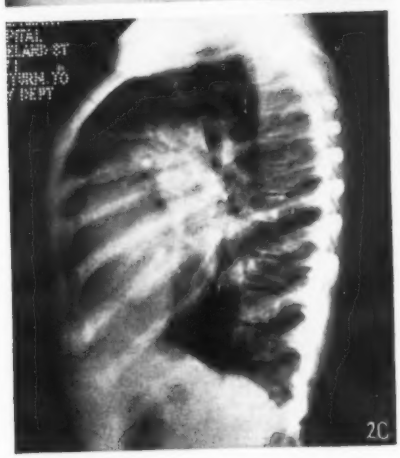


FIG. 2.—Three cases of moderate chest deformity (V.S.D. type).

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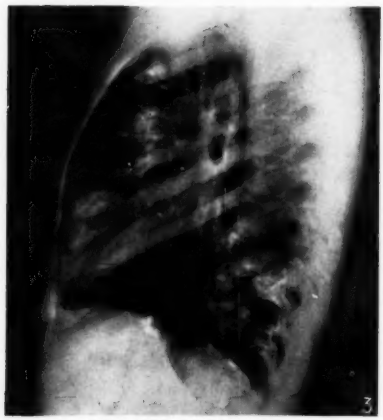

FIG. 3.—Normal lateral chest X-ray of patient with V.S.D.

FIG. 4.—Case of A.S.D. showing that sternum appears bifid on account of unilateral protuberance.

TABLE II.—HÆMODYNAMIC DATA IN 45 CASES OF V.S.D. (PULMONARY INDEX IN LITRES/MIN./M². RESISTANCE IN DYNES-SEC.-CM.$^{-5}$-M²

Case number	*Pulmonary artery pressure (mm.)*	*Pulmonary flow / Systemic flow*	*Pulmonary index*	*Total pulmonary resistance*	*Severity*
1	55/30	2·5	9·3	370	Severe
2	100/50	4·5	?	?	,,
3	90/55	1·6	8·0	700	,,
4	35/20	2·4	13·2	150	,,
5	80/50	3·0	12·8	400	,,
6	90/45	2·3	8·3	600	,,
7	95/55	2·0	7·5	800	,,
8	90/50	2·0	7·4	680	,,
9	85/45	1·3	5·5	850	,,
10	100/50	1·7	8·3	650	,,
11	90/50	2·0	8·5	600	,,
Average	58 (mean)	2·3	8·9	580	
12	80/45	2·8	14·8	300	Moderate
13	90/45	3·1	9·0	550	,,
14	80/30	1·5	4·0	950	,,
15	55/20	1·6	10·0	250	,,
16	80/30	5·0	16·5	225	,,
17	115/55	4·0	14·0	425	,,
18	80/50	1·7	6·6	725	,,
19	70/40	1·6	7·5	550	,,
20	95/50	1·6	9·6	550	,,
21	90/55	2·0	15·4	350	,,
22	95/60	?	?	?	,,
Average	57 (mean)	2·5	10·7	485	
23	30/15	3·0	25	50	Absent
24	80/25	4·4	15	225	,,
25	15/8	1·8	5·6	150	,,
26	15/6	1·5	?	?	,,
27	18/5	2·1	7·5	100	,,
28	20/10	8·0	23·5	50	,,
29	17/5	2·7	12·2	60	,,
30	65/30	2·5	7·5	450	,,
31	25/15	1·2	6·3	250	,,
32	40/15	2·6	7·2	200	,,
33	35/5	1·6	6·5	200	,,
34	25/10	1·3	5·0	250	,,
35	20/10	1·1	3·6	300	,,
36	55/20	4·0	10·1	250	,,
37	110/65	1·9	5·1	1250	,,
38	55/30	8·0	35·0	100	,,
39	25/15	1·4	6·7	225	,,
40	65/50	3·0	7·7	575	,,
41	70/40	1·3	6·5	600	,,
42	55/25	3·2	10·7	250	,,
43	25/10	4·5	20·6	60	,,
44	85/45	3·3	10·0	450	,,
45	50/20	1·4	4·0	600	,,
Average	28 (mean)	2·9	11·0	300	

Table II gives details of the cases of V.S.D. and relates the findings to the hæmodynamic data obtained at cardiac catheterisation. Of the 11 cases with severe chest deformity, all had marked pulmonary hypertension (defined simply as an elevated pulmonary artery pressure) except one (case 4). This was the youngest patient, being aged 3; his pulmonary flow was high though the resistance still relatively low.

In this group all had an increased pulmonary blood flow (average 8·9 lit./min./m^2), and all save one an increased pulmonary vascular resistance (average 580 dynes-sec.-cm.$^{-5}$-m^2).

Of 11 cases with moderate chest deformity, all had pulmonary hypertension (average mean pulmonary artery pressure 57 mm. Hg). The average pulmonary blood flow was 10·7 lit./min./m^2, and the average pulmonary vascular resistance was 485 dynes-sec.-cm.$^{-5}$-m^2.

Of 23 cases without marked chest deformity, only 6 had a mean pulmonary artery pressure greater than 35 mm. Hg; the average was 28 mm. Hg. The average pulmonary blood flow was 11·0 lit./min./m^2, and the average pulmonary resistance 300 dynes-sec.-cm.$^{-5}$-m^2.

It is evident, therefore, that this type of chest deformity (V.S.D. type) occurs in about one-half of the cases of V.S.D. analysed on the basis of the lateral chest X-ray. In this group the mean pulmonary artery pressure and total pulmonary resistance are approximately twice as high as in the group in which the deformity is mild or absent.

Eisenmenger's Complex

Six cases fulfilled the necessary criteria of an adequate lateral X-ray and hæmodynamic data, and in these the deformity was present to moderate degree in only one. The other five had normal chests. This finding is in keeping also with clinical observation.

Discussion

Why should there be such a difference between the chest configuration of the patient with an A.S.D. and the one with a V.S.D.? In the case of the former lesion, the deformity is explicable on the basis of direct pressure by the enlarged right ventricle on the malleable structures of the thoracic cage in childhood. The bulge occurs in the region just over the right ventricle. (Recently a patient with an A.S.D. was seen in whom the heart lay to the right of the sternum; in this case the bulge was right-sided.) Why the deformity occurs in some cases of A.S.D. and not in others is not clear, but may be related to the age at which significant right ventricular enlargement occurs, in that it is highly likely that the left-to-right shunt is not present at birth, but develops during the first year of life in cases of A.S.D.

Examination of cases of V.S.D., however, and consideration of their X-rays leads to the conclusion that the sternal protuberance in question is not contiguous with the heart or great vessels, and cannot be explained by the factor of

direct pressure. The only acceptable explanation must, nevertheless, be based on the idea that the mechanical forces at work in the thorax are different from those in normal children. These forces may be intracardiac or extracardiac. Certainly, the V.S.D. differs from the A.S.D. in that a left-to-right shunt at ventricular level is present, and that from birth. It is not commonly realised that the inter-ventricular septum lies virtually in the frontal plane, *i.e.* parallel to the anterior chest wall, not at right-angles to it. The right ventricle lies anterior to the septum, and the left ventricle posterior to it. Hence a shunt which is functionally left-to-right is anatomically postero-anterior, and the jet of blood is thrust forwards and upwards, towards the region where the protuberance occurs. It is theoretically possible that this abnormal force could be transmitted to the chest wall and so lead to the deformity in question. However, this seems unlikely to be the explanation on several counts. First, the V.S.D. deformity is strictly bilateral, while the heart is not. Secondly, the deformity occurs much more commonly in association with a high pulmonary vascular resistance than with a low one; most cases with a large left-to-right shunt but low pulmonary vascular resistance have normal chests (*e.g.* cases 28, 38 and 43). Thirdly, it seems unlikely that the spongy lung tissue which intervenes between the heart and the upper sternal region would be a sufficiently good mechanical conductor to cause bony deformity. Fourthly, the elastic recoil of the heart would limit this factor.

The cause of the phenomenon must, therefore, be sought in the extra-cardiac forces of the thorax, and these, of course, are related to respiration. The respiratory difficulty which occurs after surgery for V.S.D. has been mentioned already, and is one of the major problems which must be faced in the care of these cases. In some centres (Lillehei, 1959) the question is taken so seriously that a pre-operative tracheostomy is performed, the trans-sternal incision has been abandoned in favour of a vertical sternal-splitting one which does not involve the pleural cavities, and mechanical aids to respiration are employed post-operatively. It seems logical to ask, therefore, whether or not the deformity in question is related to the mechanical properties of the lungs and the work of breathing. If this were so, it would adequately explain why the bulging is strictly bilateral, why the anteroposterior diameter of the chest is increased, and why there is often sucking-in of the lower ribs. The problem therefore devolves on the mechanical properties of the lungs in cases of V.S.D. This information is not at present available, partly, no doubt, because it is notoriously difficult to perform pulmonary function studies on children. Any reasoning must, therefore, be based on hypothesis rather than fact.

On theoretical grounds, it is possible that two factors should operate in these cases to alter the mechanical properties of the lungs. The first of these is the presence of an increased amount of blood in the lungs. The second is that the pulmonary vasculature is abnormal and contains an increased amount of muscle. The ramifying branches of the pulmonary artery serve as a scaffolding for the pulmonary architecture, and increased stiffness of this scaffolding would lead to changes in the physical properties of the lungs. Separately, these two factors may have a variable effect, perhaps none. Thus, the pulmonary blood

content in atrial septal defect may be very large without making any great difference to pulmonary function. Likewise, some cases of pulmonary hypertension may be associated with relatively normal pulmonary function, as measured by the techniques currently available. Together, however, these two factors could operate to produce changes in the mechanical properties of the lungs, in a manner analogous with such variations in erectile tissue.

McIlroy and Apthorp (1958) have studied pulmonary function in patients with pulmonary hypertension and found, in general, a variable reduction in lung compliance, diffusing capacity and ventilation equivalent, with slight increase in inspiratory resistance. Their cases included five with V.S.D., but all these were in the " Eisenmenger group " and none had a pulmonary flow greater than the systemic. In only one of these cases (case 12) was the lung compliance reduced (*i.e.* the lungs being " stiffer " than normal). This is in keeping with the observation that a chest deformity is present in only a minority of patients with the " Eisenmenger syndrome " (as defined by Wood, 1958), and supports the contention that in these cases the raised pulmonary vascular resistance is present from birth. The finding of a bulging sternum in a patient with the " Eisenmenger syndrome " would suggest that there was at one time a left-to-right shunt.

McIlroy and Apthorp (1958) found hyperventilation to be common in pulmonary hypertension. This was not abolished by oxygen, and the stimulus for it is unknown. This would undoubtedly increase the work of breathing.

That changes in the properties of the lungs could produce the chest deformity of the V.S.D. is not unlikely. The pigeon-breast, with raised sternum, increased antero-posterior chest diameter, and indrawing of the lower chest wall occurs classically in rickets, being here the response of abnormal bone to normal respiratory forces. (This sternal protuberance was recorded as early as 1645 by Whistler.) Naish and Wallis (1948) found, in a study of Harrison's grooves, that they were much commoner in children suffering from asthma than in normal ones, and that their depth depended on how early the disease had started. They also found the grooves to be present in 23 out of 36 cases of congenital heart disease, though the details of diagnosis are not clear. The grooves were also noted frequently in children with a pigeon-breast deformity. A few years earlier, Naish (1945) had recorded marked inspiratory indrawing of the lower intercostal spaces in eight cases of congenital heart disease, seen in infancy, in whom there was no evidence of rickets or of upper respiratory tract infection. This is seen not infrequently in small children with V.S.D.

Sheldon (1938) noted the forward bulging of the sternum and costal cartilages in young infants with congenital heart disease, and ascribed it to cardiac hypertrophy. He made the point that there may be collapse of the bases of the lungs due to enlargement of the heart, and noted that in these infants the character of the breathing is often peculiar. It is impossible to deny that this explanation, based entirely on the mechanical effects of an enlarged heart, may be correct. It has the merit of suggesting abnormality of the respiratory apparatus, but is probably an oversimplification.

If it were correct that the lungs were stiffer than normal in V.S.D., it would

be expected that the sternal bulging would occur in any case where the essential hæmodynamic requisites are met, viz. increased pulmonary vascular resistance and increased pulmonary blood flow. These factors are present in some cases of patent ductus arteriosus, and indeed the deformity was seen in one such patient. The elevation of the sternum and the insucking of the lower ribs were very marked, as was hyperventilation. This child, aged 3, was operated upon and at the time the surgeon's unsolicited remarks were that "the lungs were stiff." She died soon afterwards. The situation in atrioventricularis communis is similar to that in V.S.D., and the deformity is also seen with this lesion, as it is when a V.S.D. is present together with other lesions, such as patent ductus arteriosus and coarctation of the aorta. In practice, however, the majority of patients with the high sternal protuberance have a V.S.D.

That there may be other factors, not at present apparent, is shown by consideration of case 4, who had severe deformity without much pulmonary hypertension, and cases 37 and 40, who had pulmonary hypertension with increased resistance and flow, but no significant chest deformity. Thus, more work must be done in the study of these deformities before any conclusions become absolute, particularly in relation to pulmonary function and the work of breathing.

Summary

The chest deformity associated with the A.S.D. differs clinically and radiologically from that of the V.S.D. In A.S.D. there is a unilateral bulge which lies directly over the right ventricle and is considered to be due directly to the pressure of this enlarged chamber. In V.S.D. there is a bilateral upper sternal protuberance, the antero-posterior diameter of the chest is increased, and there is a tendency for the lower ribs to be drawn in on inspiration.

The " V.S.D. type " deformity was found, on a radiological basis, in one-half of 45 cases of V.S.D. in whom an adequate lateral X-ray of the chest was available, together with cardiac catheterisation data. Thus, the incidence of the " V.S.D. type " deformity in cases of V.S.D. is approximately the same as that of the " A.S.D. type " deformity in cases of A.S.D.

In the V.S.D., the deformity, which is similar to a pigeon-breast deformity, was associated in most cases with pulmonary hypertension. It is considered to be much commoner when the pulmonary vascular resistance is raised than when it is not. It occurs in the " Eisenmenger syndrome " in only a minority of cases.

It is suggested that the deformity of the V.S.D. may be due to changes in the mechanical properties of the lungs, and that the combination of increased pulmonary vascular resistance and increased pulmonary blood flow increases the stiffness of the lungs.

I am much indebted to Dr. S. Gilbert Blount Jr., of Denver, Colorado, for permission to use data from a number of his cases; to Drs. Paul Wood and Aubrey Leatham of the National Heart Hospital, London, for like kindness; and to Drs. Peter Kerley and William Evans for their helpful advice.

REFERENCES

LILLEHEI, C. W. (1959): *J. thorac. Surg.* (In the press.)
McILROY, M. B., and APTHORP, G. H. (1958): "Pulmonary Function in Pulmonary Hypertension," *Brit. Heart J.*, **20,** 397.
NAISH, A. E. (1945): *Arch. Dis. Childh.*, **20,** 185.
NAISH, J., and WALLIS, H. R. E. (1948): "The Significance of Harrison's Grooves," *Brit. med. J.*, **1,** 541.
SHELDON, W. (1955): "Diseases of Infancy and Childhood," 7th ed., p. 430. London: J. & A. Churchill.
SWAN, H., KORTZ, A. B., DAVIES, D. HYWEL, and BLOUNT, S. GILBERT Jr. (1959): "Atrial Septal Defect Secundum," *J. thorac. Surg.*, **37,** 52.
TAUSSIG, H. (1947): "Congenital Malformations of the Heart." (Commonwealth Fund) New York.
WHISTLER, D. (1645): Noted by Naish and Wallis, 1948.
WOOD, P. (1958): "The Eisenmenger Syndrome," *Brit. med. J.*, **2,** 701 and 755.

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THE VALUE OF CINE-ANGIOCARDIOGRAPHY IN CONGENITAL HEART DISEASE

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Introduction

Conventional angiocardiography is established as a rewarding diagnostic procedure in modern cardiology. Cine-angiocardiography, however, is practised only in a few centres in the world and it has mainly been applied to the investigation of congenital heart disease in infants and children (Lind and Wegelius, 1955; Astley, 1957).

Cine-angiocardiography has been performed in forty-seven cases of congenital heart disease, both in adults and children, at St. George's Hospital, London. Its value in congenital heart disease will be assessed on our own results and by referring to the published work in this field.

Apparatus and Technique of Cine-angiocardiography

The patient is catheterised on a Philips catheterisation table. Both cardiologist and radiologist screen simultaneously through a two-way periscope viewer mounted on a 5-inch Philips amplifier.

Cine-angiocardiography is performed immediately after catheterisation on the same table. The total examination time is prolonged only by ten to fifteen minutes. The catheter used for measurements of pressure possesses a single end-hole; this is changed for one having multiple side holes with the tip blocked. This form of catheter will not move during the rapid injection of opaque medium, and damage to the myocardium from a single powerful jet is prevented.

Seventy-six per cent. Urografin has been found the most satisfactory contrast medium for injection. No complications have occurred in our series of twenty-five dog experiments and in seventy human subjects. As a precautionary measure, a test dose of 0·5 to 1·0 ml. of the opaque medium is given intravenously the night before the examination. 1 to 1·5 ml. of medium per kilogram body weight, warmed to body temperature, must be injected through the catheter in 1 to 1·5 seconds. The aim is to inject fast enough to obtain a concentrated bolus of medium entering the appropriate cardiac chamber and yet spread over sufficient time to ensure good visualisation in both systole and diastole. The injection is performed by a simple compressed air injector.* The pressure required to inject the whole dose of medium in less than 1·5 seconds depends on the quantity and viscosity of the medium and on the internal diameter and length of the catheter and this is determined experimentally.

Angiocardiography is always performed selectively through the cardiac

* Manufactured by Talley Anæsthetic Equipment Ltd., 37A New Cavendish Street, London, W.1.

(*Received for publication December* 8, 1958.)

catheter, the tip being placed in the site of election for the particular lesion being investigated. In most cases the cardiac abnormality has been localised at the catheterisation from the pressure readings and the oxygen saturation values. The patient is turned into the optimum radiographic position. The site of the catheter tip is finally checked by taking the pressure and by injecting a small quantity of the medium which is viewed through the periscope.

A 35 mm. Arriflex camera is then mounted on the intensifier in place of the periscope (Fig. 1).* A monocular viewer enables the radiologist to screen through the shutter of the camera. This allows him to centre the intensifier screen accurately over the heart and to follow the course of the opaque medium during the cine-angiocardiogram. The Arriflex camera is capable of various speeds from 8 to 60 frames a second, but 32 frames a second are used unless very rapid intracardiac events are anticipated.

A Philips DCX generator (output 200 mA at 100 kV) supplies a smoothed current to the undercouch tube. A stationary grid is essential and 0·25 copper filtration is employed.

Exposure is controlled by a milli-voltmeter connected to a photo-electric cell, mounted in the intensifier. Radiographic factors vary from 10 to 40 mA, at 85 to 100 kV, and the exposure time is usually between 5 to 10 seconds. Tri-X is a fast film made by Kodak and gives satisfactory contrast without too much grain.

The 35 mm. film is processed and 16 mm. copies are made in thirty-six to forty-eight hours.† The original film is kept as a master copy and the 16 mm. film is projected for diagnosis. The 16 mm. Specto projector allows the film to be shown at 16 frames a second (half the filming speed), or 2 frames a second, and the film may be stopped at any single frame.

The advantages of using the reduced 16 mm. copies for projection include:

1. The 35 mm. master film is thus preserved undamaged by repeated projection, from which unlimited 16 mm. copies can be made.
2. 35 mm. projectors are expensive and their use is subject to certain legal regulations.
3. The 16 mm. copy has a black surround and this excludes extraneous light during projection.

Clinical Application of Cine-Angiocardiography

The special advantages and the limitations of cine-angiocardiography will be discussed under the headings of the common congenital cardiac lesions.

Pure Pulmonary Stenosis with Normal Aortic Root

In pure pulmonary stenosis there is narrowing of the pulmonary valvular orifice or of the outflow tract of the right ventricle without a ventricular septal defect.

* All figures referred to in the text appear on Plates IX and X.
† By George Humphries and Co. Ltd., 71 Whitfield Street, London, W.1.

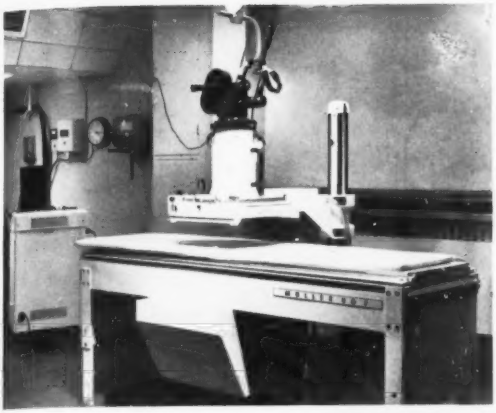

FIG. 1.—Illustration of the catheterisation table, image amplifier and 35 mm. cine-camera.

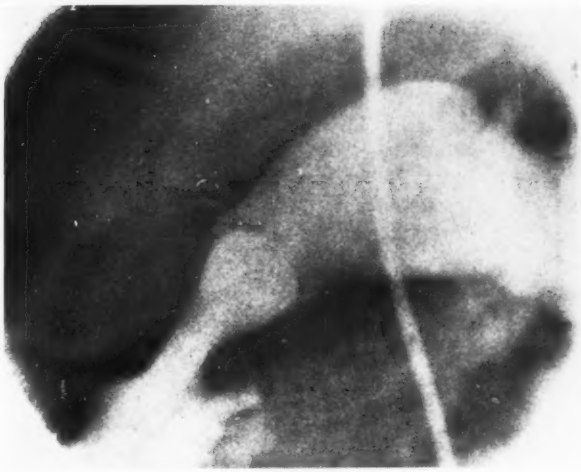

FIG. 2.—Case 1. Male aged 13 years. Left anterior oblique view. Dome-shaped deformity of the pulmonary valve with a central orifice. Post-stenotic dilatation of the main pulmonary artery. Contracted state of the outflow tract of the right ventricle, resembling infundibular stenosis.

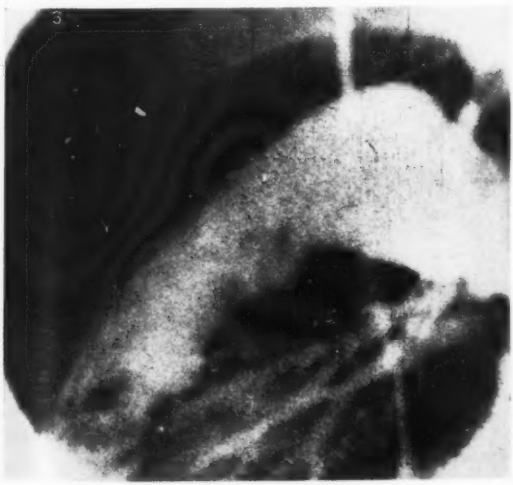

FIG. 3.—Case 1. Momentary dilatation of the right ventricular outflow tract, which occurred only in 2 frames. (Film taken at 32 frames a second.) No infundibular stenosis found at pulmonary valvotomy.

The author wishes to point out that the illustrations are copied from 35 mm. cine-film, which has a comparatively large grain size.

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FIG. 4.—Case 2. Male aged 5 years. Left anterior oblique view. Isolated infundibular stenosis. The narrowing is seen at the typical site at the junction of the inflow and outflow tracts of the right ventricle.

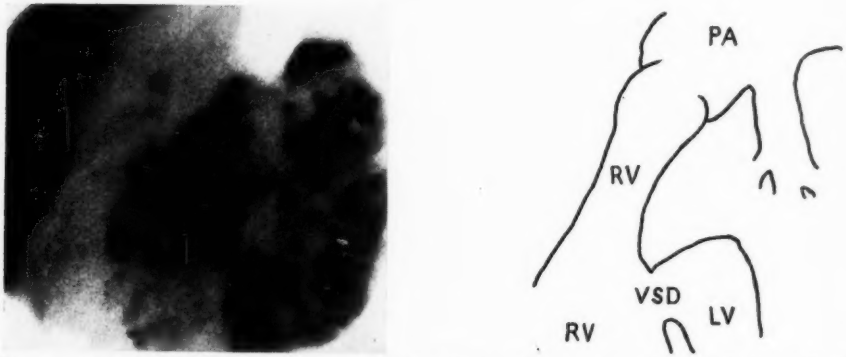

FIG. 5.—Case 3. Female aged 11 years. Left anterior oblique view. A clinical diagnosis of V.S.D. was made from a pansystolic murmur heard at the left sternal edge. Normal pressures and oxygen saturations were found at cardiac catheterisation. The cine-angiogram shows a right to left shunt at ventricular level after injection of medium into the right ventricle.

FIG. 6.—Case 4. Male aged 2 years. Left anterior oblique view. Fallot's Tetralogy. Medium injected into the right ventricle crosses the V.S.D. into the left ventricle. The very poor filling of the outflow tract of the right ventricle is consistent with marked infundibular stenosis. This was confirmed at autopsy.

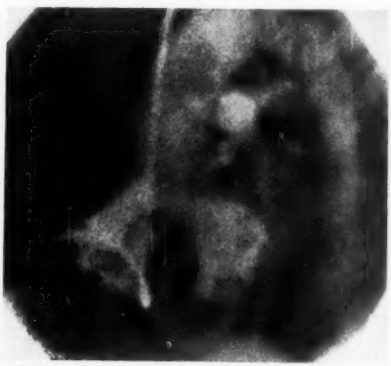

FIG. 7.—Case 4. Later stage in the cine-angiogram, showing the aorta over-riding the ventricular septum. The main pulmonary artery and its branches are small.

The pulmonary valves in pulmonary valvular stenosis are fused and form a cone or dome which projects into the pulmonary artery. The main pulmonary artery, and sometimes its left branch, usually shows post-stenotic dilatation. The abnormal valves may be smooth or irregularly thickened. The orifice usually lies centrally, but it may be eccentric; its size varies from a few millimetres to about one centimetre in diameter. It is, however, as important to obtain a clear anatomical and dynamic picture of the outflow tract of the right ventricle as it is of the abnormal pulmonary valves. In pulmonary valvular stenosis there may be an associated abnormality of the infundibulum, which is shorter and smaller than normal (Brock, 1957). In addition, the infundibular muscle, including the crista supraventricularis and its two bands, hypertrophy in response to the valvular obstruction. This adds a secondary acquired muscular obstruction to the valvular stenosis. It is vital to differentiate between this muscular narrowing and a true congenital infundibular stenosis. There is evidence that muscular narrowing, although sometimes responsible for an elevated right ventricular pressure immediately after operation, will slowly regress, provided the pulmonary valvotomy has been technically satisfactory (Engle *et al.*, 1958).

With muscular stenosis, the narrowing will show some variation in systole and diastole. In congenital infundibular stenosis, the obstruction is a rigid fibrous ring or diaphragm which exhibits no change in calibre during the cardiac cycle. Cine-angiocardiography gives an accurate picture of the right ventricular outflow tract because of the high picture frequency. With direct angiocardiography, it may be impossible to determine how much lumen change is occurring, particularly if the film frequency of the machine is limited.

Another pitfall in the differential diagnosis must be mentioned. During injection of the opaque medium, ventricular ectopic beats are invariable. If they occur in rapid succession, there is reduced diastolic filling of the right ventricle and the outflow tract may fail to dilate fully until normal rhythm occurs. The full dilatation may be seen for only a fleeting moment after resumption of sinus rhythm. Figs. 2 and 3 illustrate a case of pulmonary valve stenosis in which the momentary dilatation of the right ventricular outflow tract could easily have been missed without the high picture frequency of cine-angiocardiography. A diagnosis of congenital infundibular stenosis might then have been made and the surgeon advised to do an infundibular resection as well as a valvotomy.

In isolated infundibular stenosis without abnormality of pulmonary valves and with an intact ventricular septum, the rigid fibrous narrowing lies at the junction of the inflow and outflow tracts of the right ventricle. There may be post-stenotic dilatation of the outflow tract beyond the stenosis, if the ventricular muscle in this area is thin. Cine-angiocardiography will give an accurate pre-operative assessment of the abnormal anatomy (Fig. 4).

Patent Ductus Arteriosus

In patent ductus arteriosus the duct can be shown by injection of opaque medium into the aorta proximal to the site of the duct. This technique is more difficult and prone to more complications than angiography after injection into

the main pulmonary artery. Campeti *et al.* (1958) reported blanching of the pulmonary artery after injection of the opaque medium through the right heart, due to the dilution of the medium by blood flowing from the aorta through the duct. This occurred only during diastole, since the high velocity of the blood flow into the pulmonary artery in systole washed away the diluting blood. They comment that this is a valuable indirect sign of a patent ductus and that conventional angiocardiography is unreliable in demonstrating this appearance because of the limited film frequency. The diagnosis of patent ductus by re-opacification of the pulmonary artery after the passage of medium through the left heart and aorta is unreliable, as it is difficult to distinguish this from persistent opacification of the pulmonary artery which occurs in atrial and ventricular septal defects.

Atrial Septal Defect

The best method of demonstrating, angiographically, an atrial septal defect is to manipulate the catheter through the defect and inject opaque medium with the catheter tip lying well in the left atrial cavity. Since there is a very rapid passage of medium across the defect, the high picture frequency of cine-angiocardiography is ideal for visualising the size and position of the defect. The main problem is to differentiate between a septum primum and a septum secundum defect. If an edge to the lower part of the defect can be demonstrated, the presence of a septum primum defect can probably be excluded. The preoperative differentiation between these two types of atrial septal defect is of practical importance, because the complexity of a septum primum defect necessitates a more complicated operative technique.

Ventricular Septal Defect

As passage of medium across ventricular septal defects occurs rapidly, the high picture frequency of cine-angiocardiography is particularly suited to their investigation. The higher the right ventricular pressure, the more readily the medium travels across the defect from the right ventricle to the left ventricle. Nevertheless, we have shown passage of opaque medium across small interventricular defects, during systole, in four patients in whom no abnormal hæmodynamics were demonstrated at cardiac catheterisation (Fig. 5). Ectopic ventricular beats occurred throughout the injections, and it is probable that the altered ventricular pressures may have been the cause of this phenomenon, but the explanation is by no means clear.

Fallot's Tetralogy

If Blalock's operation is contemplated, the anatomy of the pulmonary arteries must be demonstrated. On the other hand, if it is decided to increase the blood flow to the lungs by enlarging the outflow tract of the right ventricle, or if a complete reparative operation is contemplated, the presence of infundibular stenosis or pulmonary valve stenosis must be established. If the stenosis is severe, most of the medium will be shunted through the ventricular septal

defect into the left ventricle and aorta. This results in poor filling of the right ventricular outflow tract and pulmonary valve area. Study by cine-angiocardiography, rather than by direct angiocardiography, is more likely to show the type of stenosis, as complete filling may only be momentary (Figs. 6 and 7).

Neonatal Cyanotic Heart Disease

Cine-angiocardiography has an important place in determining the operability of cyanotic heart disease in the newborn. Differentiation between the operable lesions, such as Fallot's tetralogy, and the more complicated inoperable lesions is often impossible by clinical methods. Intracardiac events occur extremely rapidly in the neonatal heart and, for this reason, high-speed cine-angiocardiography is especially useful.

Congenital Aortic Stenosis

It has been found possible to introduce a cardiac catheter through the aortic valves into the left ventricle, even in the presence of some aortic valve stenosis. It is considered likely that the differentiation between congenital sub-aortic stenosis and congenital aortic valve stenosis may well be possible following injection of opaque medium through the catheter lying in the left ventricle. Although we have no experience of this diagnostic problem, cine-angiocardiography should be more suitable than direct angiocardiography because of the rapid movements that occur in the region of the left ventricular outflow tract and aortic valves.

When opaque medium is injected through the catheter with its tip in the aorta just above the aortic sinuses, a good demonstration of the anatomy and movements of the aortic valves is obtained by the cine technique. This has already proved valuable in supplying useful pre-operative information to the surgeon in acquired aortic valve disease, and it is anticipated that the technique will be helpful in congenital valvular lesions.

Discussion

The present technique of cine-angiocardiography has certain disadvantages:

1. The field size of the intensifier is only 5 inches, but a number of firms are now developing image amplifiers of practical dimensions which possess larger screen sizes. The application of television techniques to image amplification provides an alternative method of enlarging the field.

2. Whereas the use of direct bi-plane angiocardiography is general, bi-plane cine-angiocardiography is not yet an established procedure except in a very few centres.

3. Definition in cine-angiocardiography is not as good as that obtained in the direct method.

In direct angiocardiography, however, it is impossible to employ a film frequency of more than 12 per second. Isolated events in the cardiac cycle are recorded, and much that is happening in the heart may be missed. In cine-angiocardiography, using up to 60 frames a second, rapid changes will be

recorded and a dynamic picture is obtained. The following are, therefore, considered particularly suitable for study by cine-angiocardiography:

1. Movements of the pulmonary or aortic valves.
2. Changes in the outflow tract of the right and left ventricles.
3. The rapid flow of medium across atrial and ventricular septal defects.
4. The events in the rapidly beating infant's heart.

Summary

Cine-angiocardiography, although possessing at the moment limitations of field size and of definition, is valuable in the investigation of congenital heart disease, as it supplies more information than direct angiocardiography about rapid intracardiac events.

I wish to thank Dr. Aubrey Leatham for his assistance in writing this paper and permission to publish cases under his care. I am grateful to Dr. J. W. D. Bull for his encouragement. To Dr. Graeme Sloman, I accord my thanks for his help. I thank Miss D. Green, who was responsible for the radiography. I also thank Miss R. Beddoe-Rees for her secretarial help.

REFERENCES

Astley, R. (1957): *Proc. roy. Soc. Med.*, **50,** 1024.
Brock, Sir R. (1957): "The Anatomy of Congenital Pulmonary Stenosis." London: Cassell.
Campeti, F. L., Gramiak, R., Watson, J. S., and Ramsey, G. H. (1958): *Circulation*, **18,** 887.
Engle, M. A., Holswade, G. R., Goldberg, H. P., Lukas, D. S., and Glenn, F. (1958): *Circulation*, **17,** 862.
Lind, J., and Wegelius, C. (1955): *Nord. Med.*, **22,** 914.

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PULMONARY ARTERIOVENOUS ANEURYSM

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Over 150 cases of pulmonary arteriovenous aneurysm are now on record, the review of 149 cases collected from the world literature by Weiss and Gasul (1954) being the most comprehensive. The first convincing autopsy report (Wilkens, 1917) described the findings in a young woman who died from intrathoracic hæmorrhage and who had three typical lesions, two in the right lung and one in the left, together with bilateral apical tuberculosis and patent foramen ovale. Sporadic autopsy reports appeared at long intervals (De Lange *et al.*, 1923; Klinck *et al.*, 1933; Neiman, 1934; Bowers, 1936), but there was no correlation of the clinical and post-mortem findings until Rodes (1938) described the case of a young man of 24 with clubbing, cyanosis and polycythæmia who had six unexplained epileptic attacks at the age of 16, and whose chest X-ray showed a dense shadow in the left mid-zone. He died following two major hæmoptyses, and at autopsy the lung lesion was shown to be a multilocular, thin-walled vascular abnormality in the left lower lobe. Even more interesting was the discovery of two similar lesions in the right middle and lower lobes which were not noted on X-ray. A year later Smith and Horton (1939) described the clinical diagnosis of a pulmonary arteriovenous aneurysm, and Hepburn and Dauphinée (1942) then reported the surgical cure of the lesion by pneumonectomy. Subsequently the accumulation of literature has been rapid, and the lesion enters the lists as a factor in differential diagnosis in connection with a wide variety of diseases in which the classical picture of clubbing and cyanosis with polycythæmia occurs. Difficulties arise, nevertheless, as acyanotic patients have been reported (Watson, 1947; Lawrence and Rumel, 1950; Lindskog *et al.*, 1950; Seaman and Soloman, 1952; Talbot and Silverman, 1952; Sloan and Cooley, 1953; and Ronald, 1954), but the clinical picture is, on the whole, remarkably constant. In younger patients the presence of clubbing and cyanosis, either together or separately, in association with an unusual lung shadow on radiographic examination should lead to further investigation which may confirm the classical clinical picture.

In the past, the X-ray appearances of pulmonary arteriovenous aneurysms have given rise to such varied diagnoses as bronchial carcinoma, pulmonary infarction, hamartoma, tuberculoma, bronchiectasis, lung cyst, chronic lung abscess and active pulmonary tuberculous infiltration. The clinical picture has been mistaken for that of polycythæmia vera, and the patient has been treated for this disease before the correct diagnosis has been made (Smith and Horton, 1939; Goldman, 1943; Jones and Thompson, 1944; and Alexander, 1945). In this respect Hirsch (1936) describes lung shadows, usually circular, which have been noted in polycythæmia vera. These shadows may persist for several weeks or months before finally resolving and are thought to

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be due to subpleural thromboses or hæmorrhages. Secondary polycythæmia due to cardiac disease, chronic pulmonary disease, Ayerza's disease, poison by heavy metals or drugs, and high altitudes, is more easily excluded. About a quarter of the recorded cases are cyanotic at birth or soon after and it is important to exclude congenital heart disease or, in the presence of diffuse lung shadows, fibrocystic disease of the pancreas (Husson, 1956).

There has been some controversy over the correct nomenclature for this pulmonary vascular shunt. It has been variously described as pulmonary varix, cavernous hæmangioma of the lung, arteriovenous angioma of the lung, pulmonary arteriovenous fistula, and cavernous pulmonary telangiectasis. Cope (1953), with convincing argument, suggests that the lesion is, in fact, due to the persistence of the primitive arteriovenous communications which are known to exist during the early development of the pulmonary circulation (Woollard, 1922), and, therefore, pulmonary arteriovenous aneurysm would appear to be the most logical designation. Whitaker (1947) showed the histology to be identical with that of the cutaneous lesions of hereditary hæmorrhagic telangiectasia (Rendu-Osler-Weber disease), and the link with this disease is further strengthened by the presence of telangiectases in the skin or other organs of about half the reported cases of pulmonary arteriovenous aneurysm. There is also a definite family history of skin lesions or of lung lesions or of hæmorrhagic episodes in about a fifth of the cases recorded. Other links are the five reported cases of pulmonary telangiectasia (Brink, 1950; Weiss and Gasul, 1954; Cooley and McNamara, 1954; and Apthorp and Bates, 1957). In this condition, which presents a clinical picture similar to pulmonary arteriovenous aneurysm, the aneurysms occur at capillary level in a diffuse telangiectasis involving the whole of the pulmonary vascular bed, and skin lesions are invariably present.

Occasionally cardiac and other pulmonary lesions co-exist with pulmonary arteriovenous aneurysm. Two cases of congestive heart failure have been reported, one with associated hypertension (Cleland, 1948; Brink, 1950), and two cases of simple cardiac hypertrophy (Sisson, 1945; Alexander, 1945). Two cases with coexistent mitral stenosis are also on record (Lindgren, 1946; Cope, 1953). Associated pulmonary lesions are more unusual and it has been possible to discover only two cases in the literature with evidence of other lung disease. In each case this was pulmonary tuberculosis, the first being demonstrated at autopsy (Wilkens, 1917) and the second being considered radiologically healed disease (Ronald, 1954). We have recently discovered a pulmonary arteriovenous aneurysm in a patient who was admitted following an hæmoptysis and who was found to have active bilateral upper zone tuberculosis. The tuberculous disease was brought under effective control, and subsequently the aneurysm was treated surgically with a good result.

Case Report

C.H., male aged 56, a porter, was admitted to the Chest Unit at Plaistow Hospital on 21.6.57, under the care of one of us (P.E.), having had an hæmoptysis of about 6 oz. some twelve hours previously. He had been under observation

elsewhere since July 1941 on account of a constant cough and a chest X-ray showing a wedge-shaped shadow in the left mid-zone and some fibrotic changes in the upper zones. At his initial examination (aged 40) minimal clubbing was noted, but there was no other clinical abnormality. The upper zone shadows were regarded as tuberculous, but the ætiology of the left mid-zone shadow was less certain. A bronchogram was performed in 1943 and was considered normal. In April 1946 the patient was admitted to hospital following a period of unconsciousness lasting about five minutes and preceded by paræsthesiæ and a transient paralysis of the right arm. His recovery was very rapid. A chest X-ray showed fibrocavernous tuberculosis in the right upper lobe with rather less disease in the left upper lobe and extensive reticular mottling throughout the remaining lung fields. The dense shadow in the left mid-zone was unchanged. Tubercle bacilli were isolated from the sputum. It was thought that his tuberculosis was complicated by bronchial neoplasm with probable cerebral secondaries. He was transferred to a sanatorium, where he remained until August 1947, by which time there was considerable resolution of his tuberculous disease. In 1948 gross clubbing of the fingers was apparent, and in 1952 he had a severe epistaxis. During this period he had several attacks of bronchitis and some exertional dyspnœa, but by 1952 he was becoming wheezy and his cough was more persistent. In 1953 he began to develop cyanosis which increased rapidly during the next two years and was well marked by 1955. His X-ray showed progressive fibrosis of his tuberculous lesions, but there was little change in the wedge-shaped shadow. His increasing breathlessness was attributed to chronic bronchitis and emphysema. In September 1956 he felt faint and dizzy at work but did not lose consciousness. His pulse became irregular for a short while after this incident.

On admission to hospital in June 1957 he was markedly cyanosed, his face heliotrope-hued and plethoric, with suffusion of the conjunctivæ. He was dyspnœic at rest. Gross clubbing of the fingers and toes was present. No telangiectases were seen. The heart was normal and the pulse regular. Blood pressure was 190/110. Scattered rhonchi were audible in both lung fields, but no bruit could be detected in the left hemithorax. X-ray examination revealed fibrocavernous disease in the right upper lobe and some fibrosis in the left upper lobe. A well-defined dense, homogeneous shadow was present in the left lower lobe, continuous with a tapering shadow extending towards the left cardiac border. There was some increased vascularity at the left hilum (Fig. 1).* The liver and spleen were not palpable, and no abnormality was found in the central nervous system. Tomography confirmed the left lower lobe lesion as a multilobular homogeneous shadow with a tortuous tail-like shadow extending medially (Fig. 2), best seen at 6 cm. Fluoroscopy revealed a pulsating lesion which increased in size with Müller's procedure. The blood count showed Hb=140% R.B.C.s 8·6 mill./cu.mm. Electrocardiographic examination showed some right heart strain. Sputum smears were positive for tubercle bacilli.

A tentative diagnosis of pulmonary arteriovenous aneurysm was made. He was given antituberculous therapy in the form of PAS 15 g. daily and INAH 200 mg. daily, and his chronic bronchitis and emphysema were relieved to some extent by routine therapy. By July 1957 his sputum had become free of tubercle bacilli on smear and culture. Hæmoglobin estimations varied

* The figures referred to in the text appear on Plate XI.

between 125 per cent. and 162 per cent. Oximetry tests were carried out in August, the results being as follows: Arterial saturation before O_2 administration—82 per cent.; Arterial saturation after 100 per cent. O_2 administration for 15 min.—94 per cent.

Angiocardiography was performed by Dr. J. N. Pattinson and this confirmed the solitary arteriovenous aneurysm in the left lower lobe (Fig. 3). Lung function tests in January 1958 were as follows: Vital Capacity—2,000 c.c., increased to 2,200 c.c. with adrenaline. Forced Expiratory Volume—820 c.c. increased to 1 litre with adrenaline. It was concluded that he had marked obstructive bronchial disease and possible surgical measures were considered too hazardous at that time. Prednisone was added to his antispasmodic and antituberculous therapy and his bronchospasm was relieved. Further lung function tests in February 1958 were as follows: Vital Capacity—2,500 c.c. Forced Expiratory Volume—900 c.c. Bronchospirometry—on the right side O_2 uptake was 21 per cent. and Vital Capacity was 44 per cent.

On 3.6.58 left thoracotomy was performed by Mr. J. R. Belcher. The left upper lobe contained extensive nodular tuberculosis, but the lower lobe was almost free from disease. There was an arteriovenous aneurysm 2 inches in diameter in the apical segment of the left lower lobe. A large feeding artery 0·5 cm. diameter was ligated and divided. The pulmonary vein was exposed and the draining vein, which was also enlarged, was ligated and divided. The arteriovenous aneurysm was then stripped out fairly readily from the surrounding lung, the raw area was oversewn with catgut and the chest was closed with apical and basal drains. Post-operative progress was very stormy, but his subsequent progress was good. At the time of his discharge on 10.7.58 his exercise tolerance was much greater than before operation; Vital Capacity—2,120 c.c. and Forced Expiratory Volume—850 c.c. Arterial oxygen saturation was 93 per cent. before exercise and 87 per cent. after exercise.

Further clinical examination on 28.7.58 disclosed definite subjective improvement. His dyspnœa had improved and he was able to walk further without discomfort. Clinically his general condition was much improved. There was no cyanosis, and there had been a slight recession in the finger and toe clubbing. Blood pressure was 170/90. Chest X-ray showed quiescent fibrotic tuberculous disease in the upper zones. Further examination on 13.11.58 showed complete disappearance of the toe clubbing and marked diminution of the finger clubbing. The patient's general condition was good, and although a few rhonchi were audible in the lung fields he was not wheezing. The X-ray remained unchanged. He was advised to continue on PAS and INAH, but bronchodilators were considered unnecessary. The blood count revealed Hb=103%. The mental state of the patient had improved considerably and he expressed a desire to return to work.

Discussion

The patient described here presented a difficult problem in view of his multiple chest pathology—pulmonary tuberculosis, pulmonary arteriovenous aneurysm, chronic bronchitis and emphysema. It is interesting to note the very gradual onset of the clinical signs and symptoms, and also the late age at which these occurred. Clubbing was first observed at the age of 40, a transient cerebral episode at 45, epistaxis at 51, and cyanosis was not apparent

FIG. 1.—Straight X-ray of chest showing infiltration in both upper zones and a well-defined homogenous wedge-shaped opacity in the left lower lobe (arteriovenous aneurysm).

IG. 2.—Tomogram showing a multilobular homogeneous opacity with a tortuous tail-like shadow extending medially.

FIG. 3.—Angiocardiogram showing the solitary arteriovenous aneurysm in the left lower lobe.

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until the age of 52. The complex clinical pathology and the late onset of these signs and symptoms was to some extent responsible for the late diagnosis. Initially the degree of clubbing may well have been accepted as commensurate with his chronic bronchitis and associated tuberculosis. The transient right monoplegia associated with a short period of unconsciousness is difficult to explain unless the theory of embolus arising from the arteriovenous aneurysm is acceptable, for at that time he was not cyanosed and increased blood viscosity associated with polycythæmia cannot be incriminated if it was a thrombotic episode. The whole incident was of such short duration and so dramatic that the air embolus hypothesis as postulated by Giampalmo (1950) would seem to be reasonable, for although this has not been confirmed by other workers there is no evidence that thrombi occur in these vascular abnormalities. With the onset of bronchospasm, the development of cyanosis was fairly rapid, reaching a maximum in about two years. This may be related to the known volumetric changes which occur when expiration is forced against a closed glottis (Müller's procedure), when a pulmonary arteriovenous aneurysm tends to increase in size. It was only after the development of bronchospasm that a slight increase in the size of the lung tumour could be detected, and it was presumably during this period that the shunt became sufficiently large to produce the typical cyanotic and polycythæmic changes. Apart from the increased inspiratory effort due to bronchospasm it is also likely that the increased pulmonary artery pressure associated with the emphysema was to some extent responsible for the increased size of the aneurysm in which the blood pressures are known to be relatively low owing to the dilatation of the afferent and efferent vessels connected to the peripheral sac. Even so it is unusual for cyanosis of such a degree to develop so quickly in a chronic bronchitic subject unless cor pulmonale is present, and the cardiac irregularities noted in our case in 1956 were no doubt considered indicative of right heart strain. The electrocardiogram of 1957 confirmed some right ventricular strain, but the changes were not marked.

The use of tomography and angiocardiography in the diagnosis of pulmonary arteriovenous aneurysms has been described by many authors. Although tomography can often give confirmative evidence without angiography, the latter is preferable in that it gives information not only about the radiologically obvious lesions, but also about small lesions which might easily be overlooked on a straight film or in localised tomography. That there are risks involved is well known and Sisson *et al.* (1945) described a death during angiocardiography in a case of pulmonary arteriovenous aneurysm. Multiple aneurysms have been reported in over 30 per cent. of the recorded cases, and in order to gain a really satisfactory result from surgery it is essential that all clinically significant lesions should be eradicated, even if this involves more than one operation, otherwise some cyanosis may remain, or cyanosis may develop again after the patient has apparently been cured (Janes, 1944; Lindgren, 1946; Baker and Trounce, 1948; Blades and Beattie, 1951; Charbon, Adams and Carlson, 1952). Cyanosis persisting after operation has been recorded in two cases where other lesions were unsuspected (Byron, 1948; Ronald, 1954).

In Ronald's case angiography was carried out pre-operatively and it was thought that resection of the right lower lobe lesion, which was of the diffuse type, should be curative. Five months later, when cyanosis was increasing, further angiography revealed other abnormalities in the left lower lobe not present in the previous examination. In two other instances (Sloan and Cooley, 1953—7th case; Fry *et al.*, 1958) the presence of other lesions from those resected was known, but further surgery was not advised.

The technical problems which may confront the surgeon cannot be estimated until the thorax is opened, and although local resection may be the procedure of choice it may be necessary to proceed to lobectomy or even pneumonectomy in the presence of other vascular abnormalities (Jones and Thompson, 1944). The lesions themselves vary considerably from a diffuse plexiform mass with numerous feeding and draining vessels to a single dilated coiled loop with no definite sac formation. Lindskog, Liebow, Kausel and Jansen (1950) have demonstrated several variations by their vinylite plastic bronchovascular casting technique. Satisfactory results have been obtained from the simple ligation of the feeding artery (Watson, 1947), but in the majority of cases it is necessary to perform wedge resection or lobectomy to ensure an adequate blood supply to the remaining lung tissue. Cases have been reported where there was a collateral circulation from the bronchial arteries, one case being cyanosed (Baker and Trounce, 1948; Lawrence and Rumel, 1950). It has been suggested that the majority of acyanotic cases have a collateral bronchial circulation, but this has not been confirmed at operation. Goldman (1948) describes pulmonary arteriovenous aneurysm occurring in two brothers, and at operation on the younger of these there was a definite collateral circulation from the chest wall to which the lung was adherent. In our case surgery was a particularly hazardous procedure because the aneurysm was present in the lobe of the lung least involved in a chronic tuberculous process, and the patient had only a small respiratory reserve. In spite of the immediate post-operative course his progress since has amply justified the risks taken.

That surgery is advisable is indicated by the relatively high incidence of hæmoptyses, hæmatemeses and epistaxes which may prove sufficiently severe to be fatal. Cerebral thrombosis due to increased blood viscosity is also a hazard, and neurological disturbances are relatively common. There is one case reported by Maier *et al.* (1948) where a bacterial endarteritis was superimposed on the arteriovenous aneurysm following osteomyelitis of a rib. The lesion was later excised after penicillin therapy. Dyspnœa is often dramatically relieved by surgery, and there is no doubt that the return to normal colour is, for the patient, a satisfactory psychological as well as physiological outcome.

Summary

1. The literature relating to pulmonary arteriovenous aneurysms is surveyed.

2. A case of pulmonary arteriovenous aneurysm complicated by active pulmonary tuberculosis and chronic bronchitis and emphysema, successfully treated by resection of the aneurysm, is reported.

3. The late onset of signs and symptoms in this case has been discussed in relation to the coexistent pulmonary pathology.

4. The importance of tomography and angiography as pre-operative diagnostic procedures are considered.

5. The hazards and complications occurring in the surgical approach to pulmonary arteriovenous aneurysms are reported and the reasons for considering surgical intervention outlined.

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REFERENCES

Adams, W. E. (1944): *J. thorac. Surg.*, **13,** 371.
Adams, W. E., Thornton, T. F. Jr., and Eichelberger, L. (1944): *Arch. Surg., Chicago,* **49,** 51.
Alexander, W. S. (1945): *N. Zealand med. J.*, **44,** 180.
Apthorp, G. H., and Bates, D. V. (1957): *Thorax*, **12,** 65.
Baker, C., and Trounce, J. R. (1948): *Brit. Heart J.*, **11,** 109.
Barnes, C. G., Fatti, L., and Pryce, D. M. (1949): *Thorax*, **3,** 148.
Bisgard, D. (1948): *J. thorac. Surg.*, **17,** 25.
Blades, B., and Beattie, E. (1951): *J. Mt. Sinai Hosp.*, **18,** 195.
Bowers, W. F. (1936): *Nebraska med. J.*, **21,** 55.
Brink, A. J. (1950): *Quart. J. Med.*, n.s., **19,** 239.
Burchell, H. B., and Clagett, O. T. (1947): *Amer. Heart. J.*, **34,** 151.
Byron, F. R. (1948): *J. thorac. Surg.*, **17,** 25.
Charbon, B. C., Adams, W. E., and Carlson, R. F. (1952): *J. thorac. Surg.*, **23,** 188.
Cleland, W. P. (1948): *Thorax*, **3,** 48.
Cooley, D. A., and McNamara, D. G. (1954): *J. thorac. Surg.*, **27,** 614.
Cope, G. C. (1953): *Brit. J. Tuberc. Dis. Chest*, **47,** 166.
De Lange, C., and De Vries Robles, S. B. (1923): *Ztschr. f. Kinderh.*, **34,** 304.
Denolin, H., Lequime, J., and Jonnart, L. (1950): *Acta Cardiol.*, **5,** 144.
Fry, R. M., Chapman, T. T., Shaw, K., and Wilson, R. (1958): *Irish J. med. Sci.*, **391,** 329.
Giampalmo, A. (1950): *Acta med. Scand.*, Suppl. 248.
Goldman, A. (1943): *Dis. Chest.*, **9,** 479.
(1948): *Amer. Rev. Tub.*, **57,** 268.
Hayward, J., and Reid, L. (1949): *Thorax*, **4,** 137.
Hepburn, J., and Dauphinée, J. A. (1942): *Amer. J. med. Sci.*, **204,** 681.
Hirsch, I. S. (1936): *Radiology*, **26,** 469.
Hunter, W. (1762): *Med. Obs. Soc. Phy. Lond.*, **2,** 390.
Husson, G. S. (1956): *Pædiatrics*, **18,** No. 6, 871.
Janes, R. M. (1944): *J. thorac. Surg.*, **13,** 372.
(1944): *Brit. J. Surg.*, **31,** 270.
Jones, J. C., and Thompson, W. P. (1944): *J. thorac. Surg.*, **13,** 357.
Klinck, G. H. Jr., and Hunt, H. D. (1933): *Arch. Path.*, **15,** 227.
Lawrence, E. A., and Rumel, W. R. (1950): *J. thorac. Surg.*, **20,** 142.
Lindgren, L. E. (1946): *Acta Radiolog. Stockholm*, **27,** 585.
Lindskog, G. E., Liebow, A., Kausel, H., and Jansen, A. (1950): *Ann. Surg.*, **132,** 591.
Maier, H. C., Himmelstein, A., Riley, R. L., and Bunin, J. J. (1948): *J. thorac. Surg.*, **17,** 13.
Makler, P. T., and Zion, D. (1946): *Amer. J. med. Sci.*, **211,** 261.
Neiman, B. H. (1934): *Arch. Path.*, **17,** 135.
Osler, W. (1901): *Johns Hopkins Hosp. Bull.*, **12,** 333.
Reid, M. R. (1925): *Arch. Surg.*, **11,** 25.
Rendu, M. (1896): *Gaz. des Hôp.*, **135,** 1322.
Rodes, C. B. (1938): *J. Amer. med. Ass.*, **110,** 1914.
Ronald, J. (1954): *Brit. Heart J.*, **16,** 34.
Rosack, H. P., French, S. W., and Paul, J. S. (1954): *Amer. J. Surg.*, **87,** 883.
Rundles, R. W. (1945): *Amer. J. med. Sci.*, **210,** 76.
Samson, P. C. (1948): *J. thorac. Surg.*, **17,** 23.
Seaman, W. B., and Soloman, A. (1952): *Arch. int. Med.*, **89,** 70.

SHEFTS, L. M. (1948): *J. thorac. Surg.*, **17**, 23.
SHENSTONE, N. S. (1942): *J. thorac. Surg.*, **11**, 405.
SISSON, J. H., MURPHY, G. E., and NEWMAN, E. V. (1945): *Bull. Johns Hopkins Hosp.*, **76**, 93.
SLOAN, R. D., and COOLEY, R. N. (1953): *Amer. J. Roentgenol.*, **70**, 183.
SMITH, H. L., and HORTON, B. T. (1939): *Amer. Heart. J.*, **18**, 589.
SWEET, R. H. (1948): *J. thorac. Surg.*, **17**, 23.
TALBOT, T. J., and SILVERMAN, J. J. (1952): *Arch. int. Med.*, **90**, 569.
WATSON, W. L. (1947): *Surgery*, **22**, 919.
WEBER, F. P. (1907): *Lancet*, **2**, 160.
WEISS, E., and GASUL, B. M. (1954): *Ann. int. Med.*, **41**, 989.
WHITAKER, W. (1947): *Thorax*, **2**, 58.
WILKENS, G. D. (1917): *Beitr. z. Klin. d. Tuberk.*, **38**, 1.
YATER, W. M., FINNEGAN, S., and GRIFFIN, H. M. (1949): *J. Amer. med. Ass.*, **141**, 581.

Brit. J. Dis. Chest (1959) **53**, 173.

CAVITATION IN PULMONARY SARCOMATOUS METASTASES WITH HYPERTROPHIC OSTEOARTHROPATHY

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Cavitation in one or more of multiple scattered discrete foci of pulmonary tuberculosis is common. It may also occur, but only rarely, in multiple deposits of neoplastic tissue in the lungs, and give rise to similar radiological appearances.

Efskind and Wexels (1952) reported three cases of central necrosis with the formation of cavities in tumours of Hodgkin's disease in the lungs. They refer to nine other cases recorded in the literature. The chest radiographs in their cases showed cavities surrounded by dense and irregular infiltration.

Gellman and Jelliffe (1957) reported a case of multiple cavitating pulmonary metastases secondary to a carcinoma of the tongue. In a survey of the literature they found four other examples. One with a primary in the pharynx and multiple bilateral lung metastases with cavitation in one of them (Bristowe, 1871); one with a primary in the pancreas and multiple metastatic pulmonary cavities (Salzman *et al.*, 1953); one who had a seminoma and developed multiple nodular secondary deposits which were subsequently observed to become thin-walled cavities (Salzman *et al.*, 1953); and one whose chest radiograph eight years after a resection for an adeno-carcinoma of the colon showed numerous bilateral nodules and consolidation with cavitation in the right upper lobe. Autopsy confirmed that the cavity was lined with atypical glandular epithelium, that the nodules had the same structure and that many showed central necrosis (Katzev and Bass, 1955).

Farrell (1935) reported a case in which multiple cavities demonstrated on a chest radiograph proved at autopsy to be due to breaking down sarcomatous metastases—the site of the primary was not found. Dolgoff and Hansen (1950) reported a case who, having had a Ewing's sarcoma of the femur treated by radiotherapy and amputation, developed multiple pulmonary metastases four years later and a chest radiograph at one stage showed a thin-walled cavity in one of the nodules.

A further case is now reported of a man who developed cavities in multiple lung nodules. The correct diagnosis was made difficult because, in addition to the fact that two years previously he had had a sarcoma removed from a thigh muscle, he also had been in contact with his daughter, who suffered from pulmonary tuberculosis and who had had an intermittently positive sputum for several years.

A further unusual feature of this case was the development during the progress of the disease of hypertrophic pulmonary osteoarthropathy.

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In March 1957 a man aged 51, without symptoms, was referred for further investigation because of an abnormal mass miniature radiograph.

He had attended this hospital in March 1955 because of a painful lump in the left thigh which was proved by biopsy to be a myxo-sarcoma. A pre-operative course of deep X-ray therapy (total dosage 5116r) was given at the Middlesex Hospital. In July 1955 the left rectus femoris muscle containing the sarcoma was removed.

One daughter had been in hospital on several occasions since 1948 with pulmonary tuberculosis. She had a relapse in March 1957, when her sputum was found once again to be positive.

Examination of this man showed no abnormal physical signs, but a radiograph on 6.3.57 showed two small round foci in the right lung and another small one in the left lung. These shadows were most likely due to sarcomatous metastases and this was proved at autopsy at a later date. (Fig. 1, Plate XI.)

In April 1957 a small amount of bloodstained sputum was expectorated. The daily amount gradually increased and later consistently contained large amounts of blood. Tubercle bacilli were not grown. Neoplastic cells were never demonstrated. The great majority of the cells seen in the sputum were macrophages containing lipoid and blood pigment.

In July 1957 there was an onset of lassitude which gradually increased. Serial radiographs showed the solid opacities to be getting progressively larger and a radiograph at this time showed cavitation in two of the tumours. In October 1957 all three tumours had cavitated, as may be seen in the illustration. This cavitation persisted for a further six months. The tumours then became solid again while continuing to enlarge.

In November 1957 he began to have a burning type of pain with swelling of the ankles, knees, wrists and hands, associated with a rapid development of marked clubbing of the fingers. The pain and swelling of the joints persisted, with fluctuating intensity during the remainder of his illness. Radiographs of his long bones showed evidence of the typical periosteal proliferative changes seen in hypertrophic pulmonary osteoarthropathy.

At the end of January 1958 he was admitted to hospital because of a sudden onset of pain at the base of the right lung associated with fever up to 102°, marked headache and an increase in cough with purulent sputum. Physical examination revealed a pleural rub at the right base with an impaired percussion note, diminished air entry and râles in this area. Culture of his sputum gave a profuse growth of *Strep. pneumoniæ*; white cell count was 12,500/c. mm. with 86 per cent. polymorphs. A radiograph showed a large area of consolidation to be present, adjacent to one of the larger metastases. The consolidation responded quickly to penicillin (1 mega unit twice a day for fourteen days). He was discharged in the middle of March, but had to be re-admitted in June 1958 because his general condition had markedly deteriorated. He was extremely short of breath because, although no further metastatic foci had developed, each original one had now grown to an enormous size and there was little residual functioning lung. He died on July 26, 1958.

At autopsy massive secondary tumours were found in both lungs. One in the right lung had penetrated through the diaphragm into the right lobe of the liver. In addition, metastases were found in the pancreas and in a neck muscle.

Histological sections from the tumours in the lungs, liver, pancreas and muscle showed a similar picture of spindle-shaped cells in bundles, but without any particular pattern. In some areas giant cells were fairly frequent. There were large areas of necrosis even in sections taken from the periphery of the tumours.

Hypertrophic Osteoarthropathy

Osteoarthropathy in the type of case now described appears to be a rare complication. It has occasionally been reported as a complication of primary sarcoma of the lung. Hochberg and Crastnopol (1950) reviewed all the cases of primary pulmonary sarcoma reported in the literature between 1944 and 1954. They found 71 acceptably proved cases and added 6 cases of their own. Out of this total number only 2 were complicated by osteoarthropathy. One was a malignant giant cell tumour (Gnassi and Price, 1945) and the other a lymphosarcoma (Tenezar, 1953). There has been a further case reported with this complication (Cabot case 31271, 1945). This was a fibrosarcoma of the lung which was considered to be a primary growth as there was no clinical evidence of a tumour elsewhere, but there was no autopsy.

It is, of course, a well-known complication of primary bronchial carcinoma. Ray and Fisher (1953) found 14 examples out of 139 cases of histologically confirmed lung cancer. Of these 14 cases 12 had a primary bronchial carcinoma and one had a primary rhabdomyosarcoma. In addition, one was a case with fibrosarcomatous metastases with two nodules in the left lung and one in the right lung. This latter case is of particular interest as it is similar to the one now reported, except that cavitation did not occur in the metastases. Tissue breakdown with cavitation of the tumour has not been a feature in the cases of primary sarcoma and carcinoma with osteoarthropathy.

Ray and Fisher (1953) were able to show that infection around a growth is not a factor in the development of osteoarthropathy. Out of a series of 139 cases it was from a group of 61 in which there was no clinical evidence of secondary infection that all their cases of osteoarthropathy occurred. This is probably related to the fact that 13 out of their 14 cases had growths situated in the periphery of the lung.

It is, therefore, considered that in this present case the tissue breakdown with cavitation, the secondary infection round the metastases, and the osteoarthropathy, all occurred coincidentally and that the first two factors played no part in the production of the third.

Summary

A case is reported of a man who developed multiple cavitated pulmonary sarcomatous metastases.

The interpretation of the radiographic findings was complicated by the fact that he was in contact with an infectious case of tuberculosis. Hypertrophic pulmonary osteoarthropathy developed during the course of the illness.

Acknowledgments are due to Mr. N. Matheson and Dr. G. Flatman who undertook the surgical and radiotherapy care of this patient.

REFERENCES

Bristowe, J. S. (1871): *Trans. path. Soc. Lond.*, **22,** 132.
Cabot Case 31271 (1945): *New Engl. J. Med.*, **233,** 18.
Dolgoff, S., and Hansen, R. H. (1950): *Amer. J. clin. Path.*, **20,** 974.
Efskind, L., and Wexels, P. (1952): *J. thorac. Surg.*, **23,** 377.
Farrell, J. T. (1935): *Radiology*, **24,** 444.
Gellman, D. D., and Jelliffe, A. M. (1957): *Tubercle* (*Lond.*), **38,** 280.
Gnassi, A. M., and Price, P. (1945): *Amer. J. Roentgenol.*, **53,** 582.
Hochberg, L. A., and Crastnopol, P. (1956): *Arch. Surg.*, **73,** 74.
Katzev, H., and Bass, H. E. (1955): *Dis. Chest*, **27,** 225.
Ray, E. S., and Fisher, H. P. (1953): *Ann. intern. Med.*, **38,** 239.
Salzman, E., Reid, J. H., and Ogura, G. I. (1953): *Dis. Chest*, **23,** 678.
Tenezar, F. J. (1953): *Quart. Bull. Northw. Univ. med. Sch.*, **27,** 138.

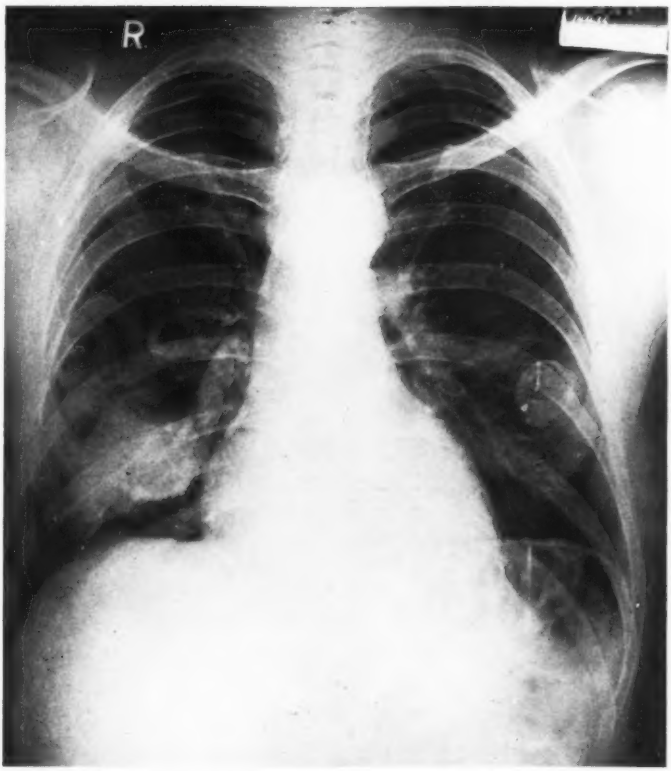

FIG. 1.—Radiograph showing cavitated sarcomatous metastases—two in the right lung and one in the left lung.

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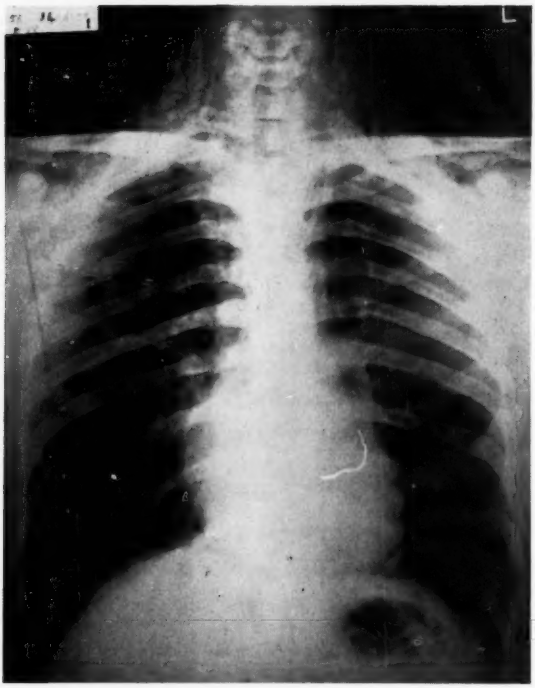

FIG. 1.—Chest radiograph showing surgical emphysema of the soft tissues and mediastinum.

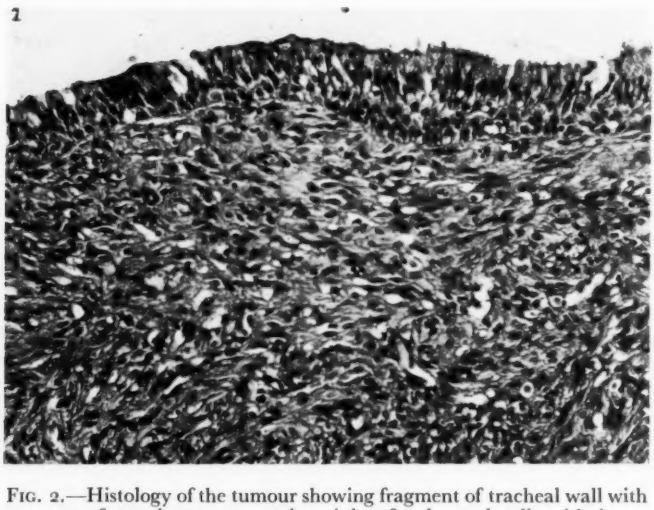

FIG. 2.—Histology of the tumour showing fragment of tracheal wall with an area of neoplasm composed mainly of polygonal cells with interlacing bundles of spindle cells.

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FIBROMA OF THE TRACHEA

M. A. L. Miller and G. A. Toma

From the Whittington Hospital, N.19

In 1767 Lieutaud described a fibroma of the trachea found at autopsy. This was the first record of a growth in this situation (Ellman and Whittaker, 1947). Since then 35 more similar tumours have been reported. (Table 1 presents a chronological recapitulation of the cases and lists the authors reviewing them.)

Table I.—Reported Cases of Primary Fibroma of the Trachea

Author	*Date*	*Total number of cases as of that date*, 48
1. Von Bruns: "Neubildungen in der Luftröhre," in von Heymann, P.: "Handbuch der Laryngologie und Rhinologie," Vienna, A. Hölder, 1898, Vol. 1, chap. 2, p. 952	1898	23
2. Krieg, E.: "Ueber die primaren Tumoren der Trachea," *Bei. Z. Klin. Chir.*, **58**, 162	1908	25
3. Lombard, E., and Baldenweck, L.: "Sur un cas de fibro-adénome de la trachée," *Ann.-d. mal, de l'oreille, du larynx*, **40**, 491	1914	29
4. D'Aunoy and Zoeller	1929	33
5. Culp	1937	36
6. Knight, J. S., and Bunting, W. P., *Arch. Path.*, **47**, 67-70, 1948 ..	1947	37

Culp completed the most recent survey of all types of primary tracheal tumours in 1936 and listed a total of 433 (Table 2). These figures increased by only three the number of tracheal fibromata reported since the comprehensive report of D'Aunoy and Zoeller in 1931.

The following case is of interest both because of the rarity of the condition and the manner in which it is presented.

Case Report

A man, aged 17, was referred to the Whittington Hospital on May 14, 1958, as a case of angioneurotic œdema, possibly requiring urgent tracheostomy.

One week previously he had come home from work breathless. He then developed progressive stridor and swelling of his face and neck. There was no past history of asthma or allergy. Three weeks before admission he said he had coughed up a "piece of flesh," accompanied by some fresh blood. A chest X-ray at that time was normal.

Clinically, on admission he appeared pale and orthopnœic but not cyanosed. He was making a peculiar singing noise with his lips on expiration. Expiratory stridor was marked. There was surgical emphysema of the eyelids, face, neck and thoracic wall. A chest radiograph showed emphysema of the soft tissues and also of the mediastinum (Fig. 1).* Urgent bronchoscopy was undertaken

* The figures referred to in the text appear on Plate XIII.

(*Received for publication November* 14, 1958.)

under general anæsthesia. A large pedunculated tumour was found about 3 cm. above the carina, virtually occluding the trachea. This was removed piecemeal. The assembled pieces measured 4×4×1 cm. There was a small pedicle on the anterior tracheal wall.

TABLE II.—DETAILS OF PRIMARY TUMOURS OF THE TRACHEA RECORDED UP TO DECEMBER 1945

Type of tumour	*Cases recorded between 1898 and 1936 (Culp, 1938)*	*Cases recorded up to Dec. 1945 (including Culp's series)*	
		Benign	*Malignant*
Papilloma	63	67	
Adenoma	9	19	
Mixed (salivary)	3	5	
Cylindroma	1	1	
Intratracheal goitre	28	31	
Carcinoma	147		187
Lipoma	5	5	
Fibroma	36	36	
Chondroma	71	75	
Osteoma			
Tracheopathi-osteoplastica			
Lymphoma	4	5	
Rhabdomyoma		1	
Giant cell tumour		1	
Sarcoma	31		34
Carcinosarcoma	1		1
Angioma	2	4	
Hæmangio-endothelioma			2
Endothelioma	1		1
Amyloid tumour	2	3	
Histology undetermined or doubtful	29		

The table gives the number of various types of primary tumour of the trachea published up to December 1945, based on Culp's (1938) figures up to June 1936, and a survey of the literature since that date.

The tracheal tumours recorded up to December 1945 can be summarised as follows:

Simple tumours	253
Carcinomata	187
Other malignant tumours	38
Tumours of doubtful histology	29
Total	507

No perforation or ulceration was seen at the site of the tumour and it was thought that the emphysema was caused by the building up of intrathoracic pressure which resulted in a leak, although the site was unknown.

The patient was immediately relieved of his symptoms and the emphysema gradually subsided.

The histological report on the tumour was:

"The tumour consists of tightly packed spindle and polygonal cells with large pale oval nuclei, relatively scanty collagen, abundant reticulin and

moderate numbers of lymphocytes. The most likely diagnosis is a cellular fibroma, but, because of the abundant reticulin, some manifestation of reticulosis cannot be excluded."

On May 23, 1958, the patient was transferred to the London Chest Hospital. Tomograms were taken and showed slight narrowing of the trachea 1 inch above the carina. A bronchoscopy was carried out and the remainder of the tumour was seen about 3 cm. above the carina. A second biopsy showed the tumour to be a cellular fibroma. It was not possible to assess the infiltrative powers of the growth.

Further exploration was undertaken on June 6, 1958, by Mr. J. R. Belcher. The tumour was approached via right thoracotomy. The base of the tumour was excised, together with about 2 mm. of the surrounding tracheal wall. The defect in the trachea was repaired without difficulty. The patient made an uneventful recovery and was discharged well on June 22, 1958.

The histological report on the specimen removed was:

"Sections show a fragment of tracheal wall with an area of neoplasm composed mainly of polygonal cells with interlacing bundles of spindle cells, as in previous sections. Tumour tissue surrounds a number of mucous glands. Tumour with mucous glands embedded separated off from other groups of glands by thin fibrous capsule. Mitotic cells not seen in these sections. Tumour is probably a benign cellular fibroma arising in the connective tissue matrix of the mucous glands." (Fig. 2.)

Discussion

Perhaps the most significant features in the clinical story were the progressive dyspnœa and widespread surgical emphysema with a marked expiratory wheeze; but there were no added sounds in the chest. The wheeze heard at the open mouth, not at the chest wall, is usually the earliest symptom, and this wheeze described by Jackson (1938) as an "asthmatoid wheeze," has often led to an erroneous diagnosis of asthma. The tumour had obviously been acting in a ball valve fashion and it was suggested that the action of the lips had been to control the rate of expiration so that the tumour would not plug the trachea. The presence of a foreign body in the trachea was considered but dismissed on bronchoscopy, and this stresses the importance of immediate diagnostic bronchoscopy in such cases, which is the only means of determining the character of the lesion or substance causing the obstruction, as well as the location and extent of a neoplastic process in the accessible bronchi, the mobility or fixity of the trachea-bronchial tree and the histological character of the lesion when biopsy is possible.

The base of the tumour together with a small surrounding area of the trachea was removed because of the risk of sarcomatous change.

Summary

A case of fibroma of the trachea which presented with interesting clinical features is described, with a review of the tracheal tumours reported in the literature up to December 1945.

We wish to thank Mr. J. R. Belcher and Mr. G. E. Stein for permission to publish this case and for their helpful advice and criticism. We are indebted to Dr. S. H. G. Robinson and Dr. K. F. W. Hinson for help on the pathological side.

REFERENCES

CULP, O. S. (1938): *J. thorac. Surg.*, **7**, 471.
D'AUNOY, R., and ZOELLER, A. (1931): *Arch. Path.*, **11**, 589.
ELLMAN, P., and WHITTAKER, H. (1947): *Thorax*, **2**, 153.
JACKSON, C., and JACKSON, C. L. (1938): *Amer. J. Surg.*, **42**, 275.
JACKSON, C., and JACKSON, C. L. (1946): " Diseases of the Nose, Throat and Ear," p. 658.
KNIGHT, J. S., and BUNTING, W. P. (1948): *Arch. Otolaryng.*, **47**, 67.
LIEUTAUD, J. (1767): " Historia anastomico-medica," Lib. IV, Obs. 64, Paris, p. 298.

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ERYTHEMA COMPONENT OF THE PRIMARY MANTOUX RESPONSE

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The development of erythema in response to intradermal tuberculin is a striking and characteristic part of the Mantoux reaction. There is, however, much evidence to show that in subjects who do not show true tuberculin sensitivity erythema may develop as a non-specific reaction. For this reason it has been repeatedly recommended that the development of erythema should not be taken into consideration in defining a positive reaction. As a result, the erythema component of the tuberculin response has tended to be neglected and the details of this part of the reaction have received less attention than they deserve. As is the case with induration (O'Grady, 1957), the erythema response may be altered by recent tuberculin testing (Forbes, 1939; Honkaanen, 1944), and the present paper deals with the erythema component of the *primary* Mantoux response—that is to say, the reaction of subjects who have either never been tested before or who have not been tested for at least three months.

Methods and Materials

The subjects tested fell into three groups:

Group 1. Non-tuberculous subjects. This group consisted of 134 patients undergoing investigation or treatment for a variety of non-tuberculous chest conditions.

Groups 2 and 3 consisted of patients suffering from active tuberculosis, subdivided according to the pattern of their Mantoux reaction (O'Grady, 1956).

Group 2. Tuberculous patients giving "normal" reactions. This group contained 138 subjects.

Group 3. Tuberculous patients giving "tuberculous" reactions. This group contained 82 subjects.

The methods of inoculation, the measurement of the responses and their classification as "normal" or "tuberculous" have been previously described (O'Grady, 1956).

Results

Form of the Erythema Component

In a typical positive response, two zones of erythema can be distinguished: reddening of the indurated plaque itself, and outlying erythema beyond the

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area of induration. Occasionally, distinct zones of different colour or intensity could be made out within the zone of outlying erythema, sometimes showing a well-marked concentric pattern as in erythema annulare. These appearances were uncommon and inconsistent and did not usually reappear when the patient was re-tested.

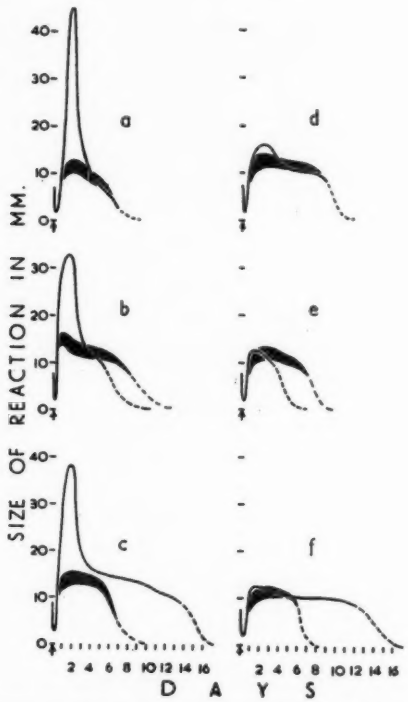

FIG. 1.—The thick line indicates induration; the lower edge of the curve shows the diameter, and the thickness of the line the depth of induration. The overlying thin line shows the diameter of erythema.

a, *b* and *c*: reactions in which maximum erythema was much greater than induration and lasted (*a*) same, (*b*) shorter and (*c*) longer time than induration. *d*, *e* and *f*: reactions of durations corresponding with *a*, *b* and *c*, in which little erythema occurred beyond reddening of the indurated plaque.

Two principal types of erythema response were distinguished. In the first, a large area of erythema developed around the indurated plaque appearing diagrammatically (Fig. 1, *a*, *b*, *c*) as a tall peak, usually overlying the point of maximum induration. This erythema usually contracted until only the indurated plaque was red (Fig. 1, *a*), but sometimes faded while the induration remained (Fig. 1, *b*), or persistently surrounded and outlasted the induration (Fig. 1, *c*).

In the second type of response very little outlying erythema appeared and the small amount present on the first day or two usually contracted rapidly (Fig. 1, *d*), or disappeared (Fig. 1, *e*). Occasionally the redness associated with the plaque persisted long after induration had ceased to be palpable (Fig. 1, *f*).

TABLE I.—SIZE OF MAXIMUM ERYTHEMA IN POSITIVE REACTIONS

Maximum induration in mm.		*Maximum erythema in mm.*				
		6-15	16-35	26-35	36-45	45
N/N	6-11	44 (62%)	23 (33%)	2 (3%)	1 (1%)	1 (1%)
	12-17	1 (2%)	17 (30%)	11 (20%)	10 (18%)	17 (30%)
	18-23	0	0	1	0	6
TB/N	6-11	39 (50%)	27 (34%)	8 (10%)	5 (6%)	0
	12-17	6 (11%)	7 (13%)	21 (38%)	14 (25%)	7 (13%)
	18-23	0	0	3	1	0
TB/TB	6-11	29 (55%)	7 (13%)	16 (30%)	1 (2%)	0
	12-17	0	3 (13%)	5 (22%)	12 (52%)	3 (13%)
	18-23	0	0	3	1	2

N/N: Non-tuberculous subjects; " normal " responses.
TB/N: Tuberculous subjects; " normal " responses.
TB/TB: Tuberculous subjects; " tuberculous " responses.

Relation of Erythema to Mantoux Pattern in Positive Reactors

In Table I it is seen that there is an overall but not close correlation between the peak size of induration and the peak size of erythema in all groups. Generally speaking, the average peak size of erythema increased with the peak size of induration. In Table II the relation between peak size of induration and the

TABLE II.—DAY OF MAXIMUM ERYTHEMA IN POSITIVE REACTIONS

Maximum size of induration		1	2	3	4
N/N	6-11	23 (29%)	31 (39%)	24 (30%)	2 (2%)
	12-17	5 (10%)	24 (49%)	17 (35%)	3 (6%)
	18-23	0	3	1	2
TB/N	6-11	27 (35%)	33 (43%)	14 (18%)	3 (4%)
	12-17	11 (19%)	24 (42%)	21 (37%)	1 (2%)
	18-23	2	3	0	0
TB/TB	6-11	15 (32%)	21 (45%)	10 (21%)	1 (2%)
	12-17	1 (4%)	14 (54%)	11 (42%)	0
	18-23	4	1	0	2

day of maximum erythema is shown. The three groups are remarkably similar, and in each the average time to peak erythema is later in those with larger reactions.

No essential differences were detected in the form of the erythema component between " normal " and " tuberculous " reactions. There was, how-

ever, a small difference in the relative durations of erythema and induration between the groups. From Table III it can be seen that in both the groups giving " normal " responses, erythema outlasted induration in about 10 per cent of subjects. Compared with this, erythema outlasted induration in those giving " tuberculous " responses both more frequently and for longer periods.

TABLE III.—NUMBER OF PATIENTS WITH ERYTHEMA OUTLASTING INDURATION BY:

	1	2-3	> 3 days
Non-tuberculous subjects. " Normal " responses	4 (3%)	10 (7·5%)	2 (1·5%)
Tuberculous subjects. " Normal " responses ..	1	11 (8%)	3 (2%)
Tuberculous subjects. " Tuberculous " responses	2 (2·5%)	12 (14·5%)	7 (8·5%)

Erythema Component of Negative Reactions

The negative reactions studied were of two kinds: *a.* Reactions to ineffective doses of tuberculin in patients who subsequently gave positive responses to larger doses. *b.* Reactions in patients who failed to develop positive reactions to 100 t.u. The results in each of these groups have been subdivided into: 1. Those in which erythema was the sole response. 2. Those in which induration developed but did not reach 6 mm. in diameter.

TABLE IV.—MAXIMUM ERYTHEMA IN NEGATIVE REACTIONS

Maximum induration mm.	*Maximum erythema mm.*						
	0	1-5	6-10	11-15	16-20	21-25	26-30
Positive							
0	78	7	20	10	5	1	1
1-5	11	61	74	16	8	4	2
Negative							
0	115	2	2	3	1	1	
1-5	0	6	5	1			

Positive: Relation between maximum erythema and maximum induration in negative reactions to small doses in subjects who ultimately proved positive to larger doses.
Negative: Relation between maximum erythema and maximum induration in negative reactions in subjects negative to 100 t.u.

In both groups the majority of patients who failed to react with induration gave no erythematous response. In those who reacted with some induration erythema always developed, and outlying erythema was found in half the patients in each group (Table IV). There was no essential difference in the form of the erythema response between these and " normal " reactions.

Discussion

In tuberculin positive subjects there was no evidence that the form or rapidity of development of the erythema component of the Mantoux response was related either to the presence of active tuberculosis or to the " tuberculous " type of response. Although there are no very impressive differences between the distribution of peak erythema size in the three groups studied, one finding deserves comment.

Amongst those developing induration of 6-11 mm., a peak erythema size of about 30 mm. was seen in 30 per cent. of those with " tuberculous " responses but in only 3 per cent. and 10 per cent. of the other groups. Similarly, in those developing 12-17 mm. of induration, a peak erythema size of about 40 mm. was found in 52 per cent. of " tuberculous " reactors and only 18 per cent. and 25 per cent. of the other groups (Table I). The relation of this hyperactivity to the " tuberculous " form of reaction suggests (and there is some other evidence for this among the negative reactors) that florid development of erythema is more common in tuberculous than non-tuberculous subjects.

It has been previously noted (O'Grady, 1956) that erythema appeared to be more persistent in association with " tuberculous " than " normal " responses. This tendency has been confirmed in the present series (Table III), and supports the idea of hyperactivity in the erythema component of the " tuberculous " response. It may, however, be no more than a reflection of the short-lived induration of these responses.

Amongst the negative reactions, both in those subjects who ultimately proved to be positive and those who proved to be negative, erythema and induration were closely related. Of those who ultimately showed positive reactions, 64 per cent. of the patients who failed to develop induration to ineffective doses showed no erythema, and in the group negative to 100 t.u., erythema developed in only 8 per cent. of those who gave no induration. In those who reacted with some induration (but less than 6 mm.) erythema almost always occurred and outlying erythema was found in about half the patients in each group. Both erythema and induration appeared, therefore, to be responses to the same stimulus. It seems, however, from their relationships, that outlying erythema is not a simple extension of the induration response but is to some extent independent of it.

If 6 mm. is taken as the minimal size for a positive reaction, and Palmer (1952) has given some objective support for such a stipulation, the smallest zone of erythema which can be regularly recognised as outlying and independent is about 10 mm. Of the patients who ultimately proved to be positive, a considerable number responded to ineffective doses of tuberculin with 10 mm. or more of erythema (Table IV). In the whole group of those negative to 100 t.u., however, erythema of a peak size of 10 mm. or more was seen in only 6 (4·5 per cent.) cases.

Of these six cases, the two giving the greatest areas of erythema were suffering from active tuberculosis, perhaps further evidence of the increased reactivity in active disease. Of the remaining patients, one had active tuberculosis and in three the presence of active tuberculosis was satisfactorily excluded.

While fully supporting the need for a rigid definition of a positive reaction, and without criticising the validity of the criteria at present employed for practical purposes, it appears that from the analytical point of view the case against erythema as a measure of tuberculin sensitivity has been over-stated. In the present series, in 136 negative reactors, lone erythema of more than 10 mm. diameter was seen in the proven absence of active tuberculosis in only two cases. In addition, it has been shown (W.H.O., 1955) that the separation of non-specific and specific responses by their bimodal distribution, as described with induration (Palmer, 1952), can be equally effectively demonstrated with the erythema component of the response.

In the face of these findings, the view that erythema is an entirely non-specific response of haphazard appearances seems very difficult to justify.

Summary

Various forms of erythema response to tuberculin are described and reasons for believing this response to be partly independent of induration are given. There was no evidence that a particular form of erythema response occurred in the presence of active tuberculosis, but it appeared that florid erythema was seen more commonly in patients with active disease. Erythema was rare in those who failed to develop induration to 100 t.u. and it is suggested that the non-specificity of the erythema response to tuberculin has been over-emphasised.

REFERENCES

FORBES, J. R. (1938): *Guy's Hosp. Rep.*, **88,** 490.
HONKAANEN, A. (1944): *Acta med. scand.*, **117,** 145.
O'GRADY, F. (1956): *Brit. J. Tuberc. Dis. Chest*, **50,** 159.
O'GRADY, F. (1957): *ibid.*, **51,** 74.
PALMER, C. E. (1952): *Lancet*, **1,** 935.
W.H.O. (1955): *Bull. World Hlth. Org.*, **12,** 189.

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CHANGES IN ERYTHEMA AS THE INDEX OF SENSITISATION AND ACTIVATION

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Although it has been generally agreed that the development of erythema alone in response to tuberculin testing should not be accepted as evidence of tuberculin sensitivity, a number of studies on tuberculin sensitisation depend on this response (Forbes, 1938; Honkaanen, 1944). Despite frequent confirmation of the finding that tuberculin sensitisation occurs less commonly in those suffering from active tuberculosis, there has been little agreement on the value of failure to sensitise as a measure of activity of the disease. A possible cause of this disagreement is the different importance attached by various workers to erythema and induration as the determining response. It appeared of interest, therefore, to compare the behaviour of erythema and induration in repeated tests and to correlate the frequency with which these two responses gave evidence of sensitisation.

Methods and Materials

The patients studied were divided into three groups: (*a*) Those positive to 1 t.u. These were re-inoculated with 1 t.u. at intervals of 1-15 days. This group consisted of (i) 22 non-tuberculous patients and (ii) 58 tuberculous patients of whom 15 gave "tuberculous" responses (O'Grady, 1956). (*b*) Patients negative to 1 t.u. but positive to 10 t.u. These were reinoculated at intervals of 1-15 days with 1 t.u. This group consisted of (i) 43 non-tuberculous patients and (ii) 93 tuberculous patients of whom 46 gave "tuberculous" responses. (*c*) Patients negative to 1 and 10 t.u. but positive to 100 t.u. These were re-inoculated at 2-3 day intervals with 10 t.u. and after a further 2-3 days with 1 t.u. This small group contained 8 non-tuberculous and 17 tuberculous patients.

The methods of inoculation, the measurement of the responses by two observers and their interpretation were those previously described (O'Grady, 1956).

Because there is evidence that the zone of erythema which develops outside the plaque of induration—outlying erythema—is to some extent independent of induration (O'Grady, 1959), the results are presented both for *total* and *outlying* erythema. In both cases the figures represent the maximal size of erythema.

Results

It is possible that certain patients regularly develop large zones of erythema while others fail to develop erythema at all. To exclude this possibility, the

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frequency with which patients responded to both doses with erythema of 10 mm. or more, or alternatively no outlying erythema, has been compared in Tables I and IV. It is clear that patients cannot be divided into those who regularly fail to produce any erythema and those who produce florid erythema.

TABLE I.—RELATION BETWEEN OUTLYING ERYTHEMA TO FIRST AND SECOND 1 T.U.

	Erythema	
	0	⩾ 10 *mm.*
First only	3	10
Second only	12	17
Both	8	13

In Tables II and III the relationship between changes in induration and changes in total and outlying erythema are shown. There was some correlation between changes in induration and total erythema in that 9/11 patients showing increased induration showed increased total erythema. In addition, all the patients showing decreased induration showed decreased total erythema. The numbers showing increase, decrease, or no change in outlying erythema, on the other hand, are so similar that the differences are almost certainly due to chance (Table III).

TABLE II.—RELATION BETWEEN CHANGES IN TOTAL ERYTHEMA AND INDURATION ON RE-TESTING WITH 1 T.U.

		Change in erythema		
		30%+	*None*	30%−
Change in induration	30%+	9	2	0
	None	15	22	27
	30%−	0	0	5

TABLE III.—RELATION BETWEEN CHANGES IN OUTLYING ERYTHEMA AND INDURATION ON RE-TESTING WITH 1 T.U.

		Change in erythema		
		30%+	*None*	30%−
Change in induration	30%+	2	8	1
	None	26	15	23
	30%−	0	3	2

TABLE IV.—RELATION BETWEEN OUTLYING ERYTHEMA TO FIRST AND SECOND 1 T.U. SEPARATED BY EFFECTIVE DOSE OF 10 T.U.

	Erythema	
	0	⩾ 10 *mm.*
First only	9	21
Second only	5	21
Both	3	25

Sensitisation was defined as being present when the reaction to the second dose was 30 per cent. greater than that to the first. The response to both doses was recorded in terms of induration and total and outlying erythema. Increases of 30 per cent. in each of these responses are identified as; induration sensitisation, total erythema sensitisation and outlying erythema sensitisation.

Induration sensitisation was found in 7/22 non-tuberculous patients and 5/58 tuberculous patients. Both total and outlying erythema sensitisation were found in 11 patients in each group. Induration sensitisation was found only in combination with outlying erythema sensitisation and then only in 2 tuberculous patients.

Comparisons between induration and outlying erythema in the patients positive to 10 t.u. are shown in Table V. The results for total erythema were identical except that 2 patients who showed no change in induration or outlying erythema showed a 30 per cent. increase in total erythema.

TABLE V.—RELATION BETWEEN CHANGES IN OUTLYING ERYTHEMA AND INDURATION ON RE-TESTING WITH 1 T.U. AFTER EFFECTIVE DOSE OF 10 T.U.

		Change in erythema		
		30%+	*None*	30%−
Change in induration	30%+	31	16	23
	None	9	16	25
	30%−	10	4	3

The comparative efficiency of changes in induration and erythema as a means of distinguishing between active and inactive tuberculosis in the patients positive to 10 t.u. is shown in Tables VII and VIII. Of the non-tuberculous patients, 82 per cent. showed induration sensitisation, 62 per cent. total erythema sensitisation, and 48 per cent. outlying erythema sensitisation. Induration sensitisation occurred together with total erythema sensitisation in 55 per cent., together with outlying sensitisation in 39 per cent. of the non-tuberculous patients.

TABLE VI.—NUMBER OF PATIENTS SHOWING SIGNIFICANT INCREASES IN TOTAL ERYTHEMA AND INDURATION ON RE-TESTING WITH 1 T.U. AFTER EFFECTIVE DOSE OF 10 T.U.

			Erythema sensitisation			
			+		−	
			No.	%	No.	%
Induration sensitisation	+	N/N	24	55	12	27
		TB/N	12	26	9	19
		TB/TB	4	8	9	20
	−	N/N	3	7	5	11
		TB/N	7	15	19	40
		TB/TB	9	20	24	52

N/N: Non-tuberculous patients with "normal" responses.
TB/N: Tuberculous patients with "normal" responses.
TB/TB: Tuberculous patients with "tuberculous" responses.

In the corresponding patients with active tuberculosis, 30 per cent. showed induration sensitisation, 40 per cent. total erythema sensitisation, and 31 per cent. outlying erythema sensitisation. Induration sensitisation was found together with total erythema sensitisation in 17 per cent. and together with outlying erythema in 15 per cent. of tuberculous patients.

Even in the non-tuberculous patients positive to 100 t.u., induration sensitisation was uncommon down to 1 t.u. All the non-tuberculous patients showed induration sensitisation to the second 10 t.u. dose, however, and half showed erythema sensitisation in addition. Of the 17 tuberculous patients, 10 failed to develop either induration or erythema sensitisation.

TABLE VII.—NUMBER OF PATIENTS SHOWING SIGNIFICANT INCREASES IN OUTLYING ERYTHEMA AND INDURATION ON RE-TESTING WITH 1 T.U. AFTER EFFECTIVE DOSE OF 10 T.U.

			Erythema sensitisation			
			+		−	
			No.	%	No.	%
Induration sensitisation	+	N/N	17	39	19	43
		TB/N	8	17	13	28
		TB/TB	6	13	7	15
	−	N/N	4	9	4	9
		TB/N	11	23	15	32
		TB/TB	4	9	29	63

Groups as in Table VI.

TABLE VIII.—NUMBER OF PATIENTS SHOWING APPEARANCE OR SIGNIFICANT INCREASE OF OUTLYING ERYTHEMA AND INDURATION ("ACTIVATION") AT 1 T.U. SITE ON TESTING WITH EFFECTIVE DOSE OF 10 T.U.

			Erythema activation			
			+		−	
			No.	%	*No.*	%
Induration activation	+	N/N	2	5	22	50
		TB/N	1	2	13	28
		TB/TB	0	0	10	22
	−	N/N	1	2	19	43
		TB/N	1	2	32	68
		TB/TB	0	0	36	78

Groups as in Table VI.

TABLE IX.—NUMBER OF PATIENTS SHOWING SIGNIFICANT INCREASE IN TOTAL ERYTHEMA AND INDURATION ON RE-TESTING WITH 1 AND 10 T.U. AFTER AN EFFECTIVE DOSE OF 100 T.U.

			Erythema sensitisation			
			1 *t.u.*		10 *t.u.*	
			+	−	+	−
Induration sensitisation	Non-tuberculous	+	1	1	4	4
		−	0	6	0	0
	Tuberculous	+	1	1	5	2
		−	1	14	0	10

The erythema components of responses elicited after sensitisation did not differ qualitatively in any way from those of primary Mantoux reactions (O'Grady, 1959).

In comparing the frequency with which erythema and induration show activation (the appearance of a reaction at a previously negative site, the

reappearance of a faded reaction, or a 30 per cent. increase in an existing reaction, on re-testing), only the appearance of outlying erythema has been considered as a reaction separable from induration. In contrast with induration activation which was seen quite commonly, erythema activation was seen altogether in only 5 patients (Table VIII).

Discussion

There is a considerable body of evidence that increased reactions on re-testing with tuberculin occur less commonly in those with active tuberculosis than in those without (Wacz-Hockert, 1950). The possibility of using this difference as a diagnostic test has been enthusiastically upheld by some (Kogel, 1912; Honkaanen, 1944) and denied by others (Hart, 1932; O'Grady, 1957). These differences may possibly depend on the relative importance attached to induration and erythema in determining whether an increased reaction has occurred. In the present series, failure to develop induration sensitisation, in itself an unreliable test, was a better index of the presence of active tuberculosis than any test based on changes in erythema. If, in an attempt to make the test more rigorous, failure to develop increases in both induration and erythema were demanded,about half the present non-tuberculous patients would appear in the active group. The best that can be said for sensitisation as a diagnostic test is that the development of both induration and erythema sensitisation in the presence of active tuberculosis is uncommon. In the present series, only about a sixth of the tuberculous patients showed this combined change.

Hart (1932) and Westwater (1934) both observed a proportion of decreased reactions on re-testing. The possible influence of time interval between doses on the development of increased or decreased reactions has been considered elsewhere (O'Grady, 1957). It appears that differences of 30 per cent. in the outlying erythema developed to consecutive tests is not great enough to detect any real differences which may occur. In contrast with induration, in which unequivocal increases are commonly seen, changes of this degree in outlying erythema are, as Smith (1929) insisted, the result of chance.

The striking failure of outlying erythema to reappear at sites showing induration activation serves further to show the partial independence of the two responses (O'Grady, 1958). The possibility that this dissociation depends on rapid loss from the skin site of a particular component of tuberculin responsible for initiating erythema is not supported by other observations. Pepys (1955) injected tuberculin into the skin of sensitive subjects and later super-injected the sites with saline, and other agents, at various intervals. If there were particularly rapid loss from the skin site of some component responsible for erythema, this procedure should influence erythema for a shorter period than induration. In fact, induration and erythema appear to go hand in hand.

It might be expected that the dissociation observed in the present series between induration and erythema activation might also be seen in the reactions observed at old or depot skin sites with the development of primary tuberculosis (Daniels, 1943; Wassen, 1939). As far as can be judged from the reports, outlying erythema appears to develop normally in these circumstances.

The stimulus for the development of induration and erythema appears, therefore, to be the same, but the difference in the ability of tuberculin and tuberculous infection to reinstate erythema at an old tuberculin site again emphasises that their rôles in invoking sensitisation are not identical (O'Grady, 1957).

Summary

The frequency with which increases in erythema and induration gave evidence of tuberculin sensitisation in the presence and absence of active tuberculosis has been compared. Failure to develop increased induration on re-testing—in itself an unreliable guide—was a better index of the presence of active tuberculosis than any test based on changes in erythema. The frequency with which increased and decreased erythema was encountered suggests that these changes were the result of chance. When, as a result of re-testing, induration reappeared at the site of a previous test, it was rarely accompanied by erythema. The possible significance of this finding is discussed.

REFERENCES

DANIELS, M. (1943): *Lancet*, **ii**, 600.
FORBES, J. R. (1938): *Guy's Hosp. Rep.*, **88**, 490.
HART, P. D'A. (1932): Spec. Rep. Ser. med. Res. Coun., Lond., No. 164.
HONKAANEN, A. (1944): *Acta med. Scand.*, **117**, 145.
KOGEL, H. (1912): *Beitr. klin. Tuberk.*, **23**, 43.
O'GRADY, F. (1956): *Brit. J. Tuberc. Dis. Chest*, **50**, 159.
Idem (1957): Serial Mantoux Testing in Man, Thesis, London.
Idem (1959): *Brit. J. Dis. Chest*, **53**, 181.
PEPYS, J. (1955): *Clin. Sci.*, **14**, 253.
SMITH, C. H. (1929): *Amer. J. Dis. Child.*, **38**, 1137.
WACZ-HOCKERT, O. (1950): *Acta pædiat., Stockh., Supl.*, **79**.
WASSEN, E. (1939): *Beitr. Klin. Tuberc.*, **92**, 515.
WESTWATER, I. S. (1934): *Tubercle (Lond.)*, **15**, 543.

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AMBULANT CHEMOTHERAPY: A PRACTICAL ADVANCE IN THE TREATMENT OF PULMONARY TUBERCULOSIS

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The advent of effective drugs in the treatment of pulmonary tuberculosis has altered the natural history of the disease in individuals and probably also the epidemiology (Joint Tuberculosis Council, 1955). In the past, conservative treatment was the only hope of those whose symptoms brought them to diagnosis, but mass radiography has led large numbers to the tuberculosis service before they are aware of ill-health and before they are able to infect others. As a result the chest clinic is attended by many who have radiographic lesions of doubtful activity. The absence of constitutional symptoms and signs has persuaded many physicians to adopt a hopeful attitude and await the excretion of acid fast bacilli, deterioration in the X-ray appearances, or complaints of ill-health, before instituting treatment.

From the patient's point of view there are adequate reasons for remaining at work, the most important being that during the patient's stay in hospital jobs are lost, often irrevocably, promotion is compromised and the stigma of "T.B." may be affixed, effectively closing many firms to these patients when they are discharged. The financial stress to a man earning an average wage of £10 or a woman £5 a week (Ministry of Labour Gazette 1955) when deprived of their livelihood by illness is insufficiently relieved by National Insurance and National Assistance. In addition a tuberculous in-patient becomes a national liability of approximately £12 a week (Hospital Costing Returns 1954), setting aside the cost to the nation of health visitors, almoners, home helps and rehabilitation organisations.

An attempt has been made to diminish these difficulties by prescribing ambulant chemotherapy in suitable cases. That is to say, the administration of an effective combination of anti-tuberculosis drugs while disturbing the patient's life as little as possible. In this way the patient loses neither money nor position and the community is saved the loss of his skill and productivity.

Suitability for this type of treatment is suggested when radiographic evidence of disease is associated with the absence of tubercle bacilli in the sputum of an intelligent patient without signs of toxæmia, *i.e.* no constitutional disturbance and a normal sedimentation rate.

Twelve of this series fall into this category; in addition twenty-eight had tubercle bacilli demonstrated by laryngeal swab or sputum examination but refused institutional treatment although it was indicated and advised.

The economic advantages of ambulant chemotherapy defeat accurate evaluation, but an estimate of this aspect suggests that this type of treatment

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TABLE SUMMARIZING THE EFFECT OF AMBULANT CHEMOTHERAPY IN THE TREATMENT OF FORTY CONSECUTIVE CASES OF PULMONARY TUBERCULOSIS OBSERVED DURING A PERIOD OF TWO YEARS

Case No.	*Occupation*	*Sex*	*Neg.*	*Con.*	*Pos.*	*Imp.*	*Unc.*	*Tim.*	*Age*
1	Instrument maker ..	M		+		+		25	3
2	Greengrocer	M		+		+		6	5
3	Commercial traveller	M		+			+	10	4
4	Tool maker	M		+		+		12	3
5	Instrument mechanic	M	+			+		9	4
6	Railway porter ..	M		+			+	9	6
7	Tank liner	M			+	+		47	7
8	Retired clerk	M		+			+	14	7
9	Housewife	F		+		+		15	6
10	Traffic inspector ..	M		+			+	12	6
11	Engineer	M		+		+		12	7
12	Master baker	M		+		+		13	6
13	Clerk	M		+			+	2	7
14	Foundry worker ..	M		+			+	9	5
15	Publican	M		+			+	10	6
16	Secretary	F	+			+		12	4
17	Instrument maker	M		+		+		12	4
18	Truck driver	M	+			+		18	5
19	Commercial traveller	M		+		+		9	6
20	Typist	F	+			+		10	4
21	Housewife	F		+			+	12	7
22*	Cabinet maker ..	M			+			16	6
23	Clerk	M		+		+		37	5
24	Draughtsman ..	M		+			+	11	4
25	Foreman fitter ..	M	+			+		7	5
26	Café proprietor ..	M		+			+	12	6
27	Scullion	M			+		+	43	7
28	Housewife	F		+			+	29	4
29	Waiter	M	+					6	4
30	Farm labourer ..	M	+			+		6	4
31	Secretary	F	+			+		10	4
32	Painter	M		+			+	6	7
33	Gardener	M		+			+	33	6
34	Battery assembler ..	M		+		+		31	6
35	Gas worker	M		+		+		6	6
36	Housewife	F		+		+		6	5
37	Colour matcher ..	M	+			+		10	3
38	Research student ..	F	+			+		4	4
39	Aircraft fitter	M	+				+	20	4
40	Handyman	M	+			+		27	5
Totals: 8 women, 32 men			12	25	3	24	15	598 months	

* Case 22 died during treatment.

Legend: Neg: Sputum negative at the start of treatment.
Con.: Sputum conversion during treatment.
Pos.: Continuing positive and still receiving treatment.
Imp.: X-ray appearance improved during treatment.
Unc.: X-ray appearance unchanged.
Tim.: Duration of chemotherapy in months.
Age: Patient's age in decades.

when effective is cheaper by several hundred pounds per patient per year. Individual benefit in terms of happiness and independence is incalculable.

The effort of carrying out this treatment from the Windsor Chest Clinic has involved no increase in staff or expenditure.

The forty cases presented in the table are a personal series whose treatment commenced during 1953 and 1954. Many more are being treated in this way (Thompson, 1955). The technique is a logical advance from the methods of post-hospital care in common use (Dressler *et al.*, 1954; Clarke, 1953) and may be in use at other centres. The only reports found in the literature of a similar method used prior to 1956 are from Scandinavia and South America (Kristenson, 1955; Sarno and Malet, 1955).

The results assessed five years after commencing the series are gratifying and in some cases startling. Twenty-five patients who were excreting tubercle bacilli when treatment began no longer do so. The X-ray appearances have improved in twenty-four and cavity closure has been observed in case 17. Cases 27 and 1 are still undergoing treatment. The former is still active and the latter moved out of the district and broke continuity in treatment. He was found to have a positive sputum in January 1957 and is once more taking ambulant chemotherapy. His disease is at present inactive. Case 2 was admitted under pressure because his mental capability was unequal to the task of continuing ambulant chemotherapy. Case 7 has chronic bilateral excavating disease and resolutely refuses institutional treatment. Unfortunately the organism responsible for his illness is a chromogen not pathogenic to guinea pigs and insensitive to both streptomycin and INAH which have been discontinued. Case 22 deteriorated and died after sixteen months' treatment. Thus of forty cases of active pulmonary tuberculosis, thirty-six were successfully controlled by ambulant chemotherapy alone without any restriction of their normal activities and with no time lost from work and living other than that needed to attend the clinic.

The twelve cases regarded as suitable for this type of treatment have all remained inactive for more than three years. At the outset it was plain that the burden on the district nurses who would be giving injections after five o'clock would be heavy. Therefore as many patients as can tolerate it are treated with PAS and INAH made up into one cachet containing 1·5 g. of sodium aminosalicylate with 33 mg. of isonicotinic acid hydrazide. Twelve of these cachets are given daily in four divided doses. I have found that it is important before undertaking ambulant chemotherapy to choose those patients judged intelligent enough to co-operate and to take them fully into one's confidence, explaining the objects to be achieved and the method to be employed. In this way the patient and his physician are able to tackle the disease together, always a desirable arrangement, but an essential condition of success with this method.

Summary

The nature and advantages of ambulant chemotherapy are described. Forty consecutive personal cases are analysed, twelve were sputum negative

and twenty-eight were excreting tubercle bacilli when treatment began. Twenty-five were converted to the sputum-negative state. One patient died during treatment. One patient was uncontrolled and had atypical organisms. It is submitted that ambulant chemotherapy in suitable cases has domestic, social and financial advantages over conservative methods.

I wish to record my thanks to Dr. Brian C. Thompson for encouraging me to publish these observations made in the Windsor Chest Clinic and for his helpful criticism.

REFERENCES

CLARKE, O. (1952): *Brit. med. J.*, **2**, 644.
DRESSLER, S. H., ANTHONY, E. M., RUSSELL, W. F., GROW, J. B., DENST, J., COHN, M. L., and MIDDLEBROOK, G. (1954): *Amer. Rev. Tuberc.*, **70**, 1930.
JOINT TUBERCULOSIS COUNCIL; "The Changing Character of Tuberculosis." 1955, Newton Abbot, Devon.
KRISTENSON, A. (1955): *Acta. tuberc. scand.*, **30**, 195.
MINISTRY OF HEALTH: "Hospital Costing Returns." 1954, **1**, 81.
Ministry of Labour Gazette, 1955, **9**, 306.
SARNO, A., and MALET, S. C. (1955): *Hoja Tisiol*, **15**, 177.
THOMPSON, B. C. (1955): *Brit. med. J.*, **2**, 620.

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SHORT-TERM ACTH THERAPY FOR DESENSITISATION AGAINST ANTI-TUBERCULOSIS DRUGS

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Introduction

The occurrence of allergic reactions to anti-tuberculous drugs is well known. The incidence varies in different centres, but these hazards are particularly common during the first three months of treatment. Fortunately, desensitisation is possible in most cases, but the current methods are unsatisfactory. Hence a short scheme, using a high dosage of ACTH, was introduced and a preliminary report of the trial has been published elsewhere (Francis and Gupta, 1958). Since then 12 more patients have been treated.

The purpose of this paper is to discuss the technique and to analyse the results. The uniformly successful outcome of the therapy has proved the value of this method. It is suggested, therefore, that this régime should be given a trial whenever drug hypersensitivity arises.

Case Inclusion

All these cases were observed personally by one of us (S.K.G.) during the period of desensitisation. Prior to commencing therapy the procedure to be adopted was carefully explained to each patient. The drugs were withdrawn in each case as soon as an allergic state was diagnosed, because an inadvertent use of the offending drug at this time might cause serious result (Gupta, 1957). As the reactions settled, either an intramuscular, intracutaneous or oral test dose was administered to determine the offending drug. The importance of this procedure is evident in case No. 2, who was previously " desensitised " against streptomycin, although he was sensitive to *p*-aminosalicylic acid.

Scheme

Before starting the ACTH therapy, every patient was examined clinically. A special note regarding past history of peptic ulcer, mental illness, cardiovascular and renal disease was made. Care was taken to exclude foci of infection. Blood pressure and weight were recorded and followed closely in all patients. A further clinical examination was made and a skiagram of the chest taken at the end of the trial. A close observation was kept for any untoward reactions for another 72 hours. In all patients a routine scheme was followed, as shown in Table I, using both long and short-acting preparations Sixty units of Corticotrophin daily were sufficient in most cases. Higher dosage (80 and 120 units daily for two days) was necessary in two patients in the first trial (Francis and Gupta, 1958), owing to loss of potency of the particular batch. In addition, four patients received local hydrocortisone (1 per cent.).

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TABLE I.
(Patient sensitive to streptomycin)

	8 *a.m.*	10 *a.m.*	2 *p.m.*	4 *p.m.*	8 *p.m.*	10 *p.m.*
1st day	X	X	X	X	20 (L)	X
2nd day	20 (S)	PH	20 (S)	PH	20 (L)	PH
3rd day	20 (S)	½ G. SM PH	20 (S)	PH	20 (L)	PH
4th day	20 (S)	1 G. SM PH	X	PH	20 (L)	PH
5th day	20 (L)	1 G. SM PH 1 G. SM	X	PH	X	PH
6th day	Usual drugs without ACTH					

Abbreviations: X—No drugs administered.
SM—Streptomycin.
PH—*p*-aminosalicylic Acid and Isoniazid.
(S)—Short-acting ACTH (in units).
(L)—Long-acting Gel (in units).

A similar routine was followed also in cases of sensitivity to other drugs. A small quantity of the offending drug (about one-half to one-third of the daily dosage) was administered in divided dosage on the second day at 10 a.m., 4 p.m. and 10 p.m. respectively. The full dosage was restored on the third day. On the sixth day it was usually possible to discontinue the ACTH cover. In every case, however, the usual three drugs were given concurrently. There is a detailed analysis of these patients in Table II.

COMPLICATIONS

None of the cases treated so far has had any serious complication. Following withdrawal of ACTH, two elderly men developed muscular aches—one sufficiently severely to require analgesics. Many patients rapidly gained weight which was subsequently lost by diuresis. Amongst the treated cases one had a previous history of glycosuria, two had hypertension, while another had a history of peptic ulceration.

Discussion

Since the advent of streptomycin and *p*-aminosalicylic acid many untoward reactions have been reported. Some of these are toxic phenomena (such as vertigo and deafness due to streptomycin), while others result from hypersensitivity and idiosyncrasy. There is a considerable overlap between the two groups and sometimes it may be difficult to determine the exact nature of a particular symptom. The commoner manifestations of hypersensitivity are fever, rash (macular, maculo-papular, erythematous, or even purpuric), exfoliative

TABLE II

Case No.	*Age*	*Sex*	*Drug therapy before reaction*	*Nature of reaction*	*Offending drug*	*Time needed for desensitisation*	*Comment on therapy and complication*	*Follow-up*
1	61	M	PH for 4/52	Rash, headache, " Pins and needles "	P	5 days	Weight gain, diuresis, severe muscular aches	1 year.
2	60	M	SP for 3/52	Rash, conjunctivitis, nausea, headache	P	5 days	Slight weight gain, Diuresis	1 year.
3	56	M	SP for 15/52	Exfoliative dermatitis, vomiting, headache	P and S	7 days	Weight gain, diuresis, slight muscular aches	1 year.
4	52	M	SPH for 6/52	Rash, pyrexia, headache	S	5 days	No complications	9 months
5	26	M	SPH for 4/52	Rash	P	5 days	No complications	8 months.
6	59	M	SPH for 8/52	Purpuric rash, nausea	S and P	5 days	No complications	8 months.
7	27	F	SP for 11/52	Rash, conjunctivitis	S	4 days	No complications	6 months.
8	46	M	SPH for 7/52 (hypertensive pt.)	Pyrexia, rash, headache	S	5 days	No rise in blood pressure, no other complication	6 months.
9	41	M	SH for 18/52 (past history glycosuria)	Rash, headache	S	5 days	No complications	1 year.
10	20	M	SP for 6/52	Rash, headache	S	5 days	Slight weight gain	1 year.
11	54	M	SP for 5/52	Rash, headache	S	5 days	Rapid weight gain, Diuresis	1 year.
12	49	M	SP for 6/52	Rash, nausea, conjunctivitis	P	5 days	Voracious appetite and slight weight gain	4 months.

Abbreviations: S—Streptomycin.
P—P.A.S.
H—Isoniazid.

dermatitis, headache, nausea and vomiting, lachrymation and conjunctivitis, stomatitis, arthritis, lymphadenopathy, eosinophilia and jaundice (Gupta and Grant, 1958). Alarming reactions of anaphylaxis are uncommon (Welch *et al.*, 1953),but such cases have been recorded (Rosen, 1948; Gupta, 1957). Bronchospasm and asthmatoid wheeze, urticaria, angioneurotic œdema, hypotension, are ominous signs.

Various methods of desensitisation have been tried in the past (Crofton, 1953; Houghton 1954). Crofton and his colleagues (Crofton and Foreman, 1948; Crofton, 1953) advocated the slow method. In case of *p*-aminosalicylic acid, Crofton used 0·5 G. initially and reached the full dose in three weeks. He suggested streptomycin 0·1 G. as a starting dose, gradually restoring the full dose in two weeks. The slow method has the disadvantage of not providing an adequate drug cover during the period. The course is protracted and too often symptoms recur. Moreover, some of the patients develop hypersensitivity to other drugs almost simultaneously (Cuthbert, 1952; Jeffery *et al.*, 1952; Macpherson, 1957). Complete desensitisation may then need a long time, when drug-resistant bacilli may emerge (Francis and Gupta, 1958.)

Withdrawal of the sensitising drug is often practised, but this may later precipitate an anaphylactic reaction. Recently Fox *et. al.* (1957) pointed out that 5·1 per cent of newly diagnosed patients harboured bacilli resistant to one drug and a few patients were initially resistant to two. There is also a growing opinion regarding the advantage and superiority of combining the usual three drugs in every new case (Penman, 1958; Smart, 1958; personal communication).

The efficacy of ACTH and steroid therapy in suppressing drug reaction is well known (Thomas, 1955). Though unexplained, initial superiority of ACTH over cortisone and prednisone has been noticed by several observers (Duthie, 1956; Savage *et al.*, 1957). Isolated records of desensitisation with prednisone have been reported (Pines, 1957), but the results are not promising. Houghton (1954) suppressed the untoward reactions using prolonged, high dosage of ACTH—a scheme not suitable for routine use. The possibility of success with a shorter course of ACTH was suggested by Nicholson (1956).

The short-term ACTH therapy has many advantages. The course is brief so no special precaution is necessary. Complications are few and mild. Desensitisation to two or more drugs may be carried out simultaneously (as in cases Nos. 3 and 6 in this series). The patient has no break in the treatment as the drugs are administered concurrently. No drugs need to be withdrawn, so the morale of the patients remain high. The scheme is adjustable. Higher dosage of ACTH may be instituted at any time or the course may also be prolonged. No adverse effect on the disease was noted in any case. Probably cases showing signs of anaphylaxis need more care and the full dosage may be restored on the fifth day or later.

No trial was undertaken for streptomycin handlers, who probably need the slow desensitisation (Crofton, 1953; Cohen, 1954). The short-term ACTH therapy should not be used in such cases. Desensitisation is hardly possible under the cover of anti-histaminics alone (Hudson, 1957).

Summary

A critical analysis of a technique (using high dosage of ACTH for a short period) is described for desensitisation against anti-tuberculous drugs. Other techniques and their disadvantages are briefly discussed.

Mr. D. Purdie (Armour Laboratories) kindly supplied the ACTH.

REFERENCES

COHEN, R. C. (1954): *Tubercle (Lond.)*, **35**, 142.
CROFTON, J. W., and FOREMAN, H. M. (1948): *Brit. med. J.*, **2**, 71.
CROFTON, J. W. (1953): *ibid.*, **2**, 1014.
CUTHBERT, R. J. (1952): *ibid.*, **2**, 1205.
DUTHIE, J. J. R. (1956): "The Principle and Practice of Medicine," 3rd edition, p. 444. Edinburgh and London: Livingstone.
FOX, W., WEINER, A., MITCHISON, D. A., SELKON, J. B., and SUTHERLAND, I. (1957): *Tubercle (Lond.)*, **38**, 71.
FRANCIS, R. S., and GUPTA, S. K. (1958): *ibid.*, **39**, 236.
GUPTA, S. K. (1957): *ibid.*, **38**, 416.
GUPTA, S. K., and GRANT, N. M. (1959): *Post grad. med. J.*, in press.
HOUGHTON, L. E. (1954): *Lancet*, **1**, 595.
HUDSON, E. H. (1957): "Symposium on Tuberculosis," 1st edition, p. 438. London: Cassell.
JEFFERY, B., BORRIE, P., and MACDONALD, N. (1952): *Brit. med. J.*, **2**, 647.
MACPHERSON, P. (1957): *ibid.*, **1**, 505.
MCKENDRICK, G. D. W. (1951): *Lancet*, **2**, 668.
NICHOLSON, H. (1956): "Progress in Clinical Medicine," 3rd edition, p. 217. London: Churchill.
PENMAN, A. C. (1958): *Lancet*, **1**, 167.
PINES, A. (1957): *Brit. med. J.*, **2**, 202.
ROSEN, F. L. (1948): *J. Amer. med. Ass.*, **2**, 1271.
SAVAGE, O., DAVIS, P., CHAPMAN, L., POPART, A. J., ROBERTSON, J. D., and COPEMAN, W. S. C. (1957): *Brit. med. J.*, **2**, 1257.
SMART, J. (1958): personal communication.
THOMAS, L. (1955): "Textbook of Medicine," 9th edition, p. 482. Philadelphia and London: Saunders.
WELCH, H., LEWIS, C. N., KERLAN, I., and PUTNAM, L. E. (1953): *Antibiot. and Chemother.*, **3**, 91.

Brit. J. Dis. Chest (1959) **53**, 202.

REVIEWS OF BOOKS

Emotional Factors in Pulmonary Tuberculosis. By DAVID M. KISSEN. With a Foreword by Sir HENEAGE OGILVIE. London: Tavistock Publications, 1958. Pp. xvii+246. 35s.

This interesting and stimulating book, by a chest physician with some psychiatric training, reports a careful "objective" study with the laudable if perhaps over-ambitious purpose of establishing a specific personality trait as the proven psychological factor in determining the onset and relapse of pulmonary tubercle in infected persons. Dr. Kissen uses a skilful questionnaire technique on a random morbid population controlled by a well-matched sample of healthy persons and non-tuberculous chest patients. Statistical treatment of the data shows a highly significant correlation between the onset and relapse of tuberculous activity on the one hand and the emotional factor of "Break in a love link" in persons characterised by the personality trait of "inordinate need for affection" (culled from Wittkower's work, with whose conclusions the author was dissatisfied, owing to lack of controls). This trait was, however, elicited by clinical judgment and inference from evidence of what seem not very profound personality studies, if the cited case histories are the criterion. In themselves these show the incidence of "break in love link" as proving deprivation and thus an unassuaged "inordinate need" not otherwise well defined, or contrasted with healthy need for affection in the control cases.

From this Dr. Kissen builds up his theory of specificity of this trait, as contrasted with analogous "specific" personality factors such as "mother fixation" for asthma, "material insecurity" for peptic ulcer, and so on. Nobody could, after this work, doubt the reality of the emotional factor in tuberculosis—but the "specificity" for this disease of one of the most generally distributed though uncalibrated characteristics of mankind ("inordinate need for affection") has not been demonstrated to the satisfaction of at least one person. It is a pity that, despite seeking expert advice, Dr. Kissen, who is primarily a chest physician, was not aided in this valuable and painstaking study by a good personality psychologist or psycho-analyst, to bring to the psychiatric assay the same degree of sophistication as is shown in his general project design. Now, one feels, someone will have to start all over again! A brief review can do but scant justice to the many interesting findings and correlations, packed with starting points for epidemiological and psychosomatic studies. It is good that such books should be written; even if they show how much sincere and thoughtful research workers, like Dr. Kissen, are still hampered by slender resources.

H. V. DICKS.

A Practice of Thoracic Surgery. By A. L. D'ABREU. Edward Arnold Ltd. Pp. 619. Illus. £5.

Five years ago this work was welcomed as an informative and authoritative account of thoracic surgery by a surgeon who relied almost entirely on his own extensive experience. This new edition brings up to date the subject

matter and adjusts any minor shortcomings that the first edition may have suffered.

It is a monumental task for a surgeon in active practice to undertake the compilation of a complete work on a growing and considerable subject. Mr. d'Abreu uses a few collaborators for special sections such as angiocardiography and cardiac catheterisation, but in general it is the clinical and personal approach to the subject which gives the book its main attraction.

The text is freely illustrated by an admixture of line, tone and photographic reproductions. Many of these, in particular those of radiographs, are excellent. Possibly some of the smaller heart diagrams could in some future edition be clarified or enlarged.

The general balance of the book is good, the high lights dominating the picture. Wounds of the chest, emphysematous cysts and bullæ, hydatids and œsophageal atresia are little masterpieces of description, while, on the contrary, diaphragmatic hiatus hernia, tracheostomy and hæmothorax receive less attention than they deserve.

The impression that the reader will gain from this work is that it is written by an active practising surgeon who knows his craft and is prepared to impart his knowledge as freely as he can. But since no critic can avoid casting a slight dash of vinegar at a full-bodied wine, could future references be checked as regards their spelling and " vital statistics."

T. Holmes Sellors.

Manual of Chest Clinic Practice in Tropical and Sub-tropical Countries. By A. J. Benatt. Edinburgh: E. and S. Livingstone. Pp. 100. 10s. 6d.

Obviously the chest clinic serves a very different purpose in tropical countries to what we know in England. Dr. Benatt has had considerable experience, and in this little book he has tried to " help others who may have to treat tuberculosis under difficulties." He has divided it into two sections: the first deals with general principles and organisation, the second with details of techniques used in the chest clinic.

The English reader will be interested but learn little that is new: the workers in tropical clinics will find useful and detailed information about clinic procedure and certain pathological tests.

The purpose of such clinics is fourfold—prevention, diagnosis, treatment and rehabilitation—but very little mention is in fact made of treatment or follow-up based on the clinic. Yet in these areas hospital facilities are minimal. Much valuable space in this small book is wasted by repetition and by details of tests which are best sought in pathology manuals: three pages are devoted to treatment, but eighteen pages to diabetes (including diet charts) and pregnancy in the tuberculous.

Nevertheless, the wisdom and method of an experienced doctor is made available to those medical and lay workers who tackle this problem in tropical countries, especially in small rural clinics.

Owen Clarke.

Leprosy in Theory and Practice. Edited by R. G. Cochrane. Foreword by Sir George McRobert. Bristol: John Wright. Pp. 407. 84s.

Since the publication of R. G. Cochrane's " Practical Textbook of Leprosy,"

some twelve years ago, enormous strides have been made in the whole subject, especially in the realms of pathology and treatment, constituting one of the greatest achievements of medicine during the present century. At last this foul, historic, and much-dreaded scourge of mankind is being subjugated. For this happy solution the editor of the present publication must be given full credit.

In this solid volume some twenty-four authorities, all of whom have been hand-picked with precision by the editor during his world-wide wanderings, have each contributed a chapter on their particular speciality.

There are also six appendices on details, such as plastic surgery and special techniques.

Of the subject matter the editor has himself contributed, with great *réclame*, some eight chapters on the most important aspects, and each is replete with original matter and fully documented. With such a collection of first-class contributors it is difficult to select any for special praise, but for beauty of composition and illustration the chapter on General Pathology and Histopathology by V. R. Khanolkar of Bombay, the clear and valuable contribution by D. P. Choyce on the Eye Lesions, the original and instructive Radiographic Appearances and Bone Changes by D. E. Paterson, and the masterly presentation of Deformities in Leprosy (as one would expect) by Paul Brand stand out.

The format and production on art paper has resulted in a handsome volume which does credit to the publishers.

This, then, is a work of high standard which should find its way into the hands of all who take an interest in the world-wide problem of leprosy, and it is also one whose lessons cannot be neglected by specialists in its ally—tuberculosis.

PHILIP MANSON-BAHR.

Les Hémoptysies Tracheo-bronchiques. By ANDRÉ MEYER and JACQUES CHRÉTIEN. Paris: Masson et Cie. Pp. 158, 23 figures. Fr.2000.

The study of hæmorrhage which originates in the trachea and bronchi, in contrast with bleeding which arises from lung tissue, is of comparatively recent date. In fact, it is claimed that this is the first detailed report to be published.

The basis of the work is a series of 717 patients who were studied in a special clinic. In 135 of these cases it was possible to locate the cause of the bleeding in the tracheo-bronchial portion of the respiratory tract.

The authors point out that the possibility of bleeding from the bronchi rather than from the lungs was hardly recognised at the beginning of the present century. It is true that Laennec devoted a chapter to the subject in his famous monograph, but the conception was not generally accepted until long after his time.

The development of the laryngoscope, and later the bronchoscope, have completely altered our views on bleeding from the respiratory tract. It is not so long since dry hæmorrhagic bronchiectasis was separated as a distinct clinical entity, and the part played by chronic bronchitis as a frequent cause of hæmoptysis is still not commonly recognised.

JAMES MAXWELL.

XII Congrès National de la Tuberculose, Montpellier, 1958. By Professeur BARIÉTY, Secrétaire-général. Paris: Masson et Cie. Pp. 206, 22 figures. Fr.2500.

The study of pulmonary function has attracted a great deal of attention in the past ten years, and a large part of the book is devoted to a summary of the present position, with an acute accent on the contributions of French authors.

The first section is concerned with the respiratory function in pulmonary tuberculosis, with special stress laid on the vital capacity and the maximal expiratory volume per second. The changes which are found to follow the medical and surgical methods of treatment of tuberculosis are discussed.

The second section deals with the subject of rupture of caseous glands into the bronchi, and it is pointed out that this may happen a very long time after the primary infection has occurred, and that there may be no other evidence of tuberculous infection in the lungs.

The final section deals with the very important question of the risk of recurrence of the disease after chemotherapy. It is still too soon to form a definite opinion. The factors which appear to influence the occurrence of relapse are the age of the patient, the type and duration of the lesions and the rapidity of response to treatment.

The need for adequate chemotherapy is stressed. A bad result is often due to insufficient treatment.

JAMES MAXWELL.

BOOKS RECEIVED

The following books have been received and reviews of some of them will appear in subsequent issues:

Treatment of Lung Cavities and Endobronchial Tuberculosis. By Beryl E. Barsby. Edinburgh: E. and S. Livingstone. Pp. 147. Illus. 20s.

Modern Trends in Diseases of the Vertebral Column. By Reginald Nassim and H. Jackson Burrows. London: Butterworth. Pp. 292. Illus. 75s.

La Corticotherapie Surrenale dans le Traitement de la Tuberculose. By Ch. Gernez-Rieux, H. Warembourg and M. Pauchant. Paris: Masson. Pp. 216. Illus. Fr. 2,600.

Advances in Tuberculosis Research/Fortschritte der Tuberkuloseforschung/Progrès de l'Exploration de la Tuberculose. Vol. 9. Edited H. Birkhauser, H. Blach and G. Canetti. Basel/New York: S. Karger. Pp. 343. S.Fr. 64.

Health Horizon. London: The Chest and Heart Association (formerly NAPT). Pp. 56. 2s. 6d. quarterly.

Recent Advances in Respiratory Tuberculosis. By F. Heaf and N. Lloyd Rusby. 5th edn. London: J. and A. Churchill. Pp. 284. 35s.

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REPORTS

JOINT TUBERCULOSIS COUNCIL

1. A Report on the Future Service for Tuberculosis and Diseases of the Chest, October 1958

The Joint Tuberculosis Council make certain recommendations which are summarised as follows:

(A) Tuberculosis, though on the decline, still presents a problem necessitating a continued attack for the foreseeable future.

(B) Non-tuberculous respiratory disease cannot be completely divorced from tuberculosis; the techniques developed from the original pattern of Sir Robert Philip which have proved so valuable in anti-tuberculosis work can with advantage be extended to the management of other chronic respiratory disease.

(C) The total requirements of beds for treatment of tuberculosis will continue to decline in future years, but there will still be need to maintain efficient units both for tuberculous and non-tuberculous respiratory disease.

(D) The future control of tuberculous disease will depend on the recognition of the changing epidemiological pattern. The reduction and eventual elimination of the sources of infection will depend not only on the efficient treatment and long-term supervision of the tuberculous individual but also on the supervision of that individual's environment.

(E) The integration with general medicine which has already begun should be continued in the following ways:

i. Future consultant appointments to chest clinics or out-patients should include membership of the medical staff of a major general hospital.
ii. As in the case of other physicians on the staff of general hospitals, beds should be allocated to chest physicians.
iii. Efforts should continue to be made to bring chest clinics within the curtilage of general hospitals.

(F) A department of chest medicine must be in, or attached closely to, each teaching hospital.

(G) The staffing structure of the chest service requires urgent revision to bring it into line with the staffing structure of general medicine.

(H) It is imperative that confidence in the future of the chest specialty should be restored as rapidly as possible.

2. Treatment of the Tuberculous Woman in Pregnancy

The Council's sub-committee on Tuberculosis and Pregnancy has dealt with certain specific questions in relation to the different outlook in tuberculosis following chemotherapeutic advances which are briefly summarised here. The members of the committee emphasise that pregnancy to-day has no deleterious effect on tuberculosis and that, with the present régimes, in patients with active tuberculosis the disease can be controlled perfectly well. The fœtus seems to be unaffected by the maternal therapy and there is, therefore, no call for any alteration in treatment either of the tuberculous infection or of the pregnancy, and, moreover, surgery may be successfully undertaken up to the sixth month of pregnancy should this be necessary.

Concerning the termination of pregnancy, they confirm that there is no

indication, either obstetric or medical. Only in very exceptional cases, such as in those patients with severely impaired pulmonary function, adverse psychiatric reaction to the combination of tuberculosis and pregnancy, or the inability of a multiparous woman to undertake the additional work of looking after another baby without precipitating a breakdown, may termination and sterilisation have to be considered.

Concerning Chest X-rays. There were very few cases in which it would be necessary to X-ray the chest more frequently than at three-monthly intervals, and tomography and screening should be avoided during pregnancy. Routine ante-natal X-rays are advisable at the end of the thirteenth week, and where normal the only indications for a further X-ray would be if there had been direct contact with a positive sputum case, and X-rays should not be undertaken after the twenty-sixth week. There is no known risk to the mother of somatic damage following a properly conducted X-ray of the chest but, in general, chest examinations should not be repeated unnecessarily. As far as the fœtus is concerned, in the first twelve weeks of pregnancy, there is very little risk of somatic damage. The other special risk to the fœtus is that of irradiation of the gonads from "scatter" increased in vertex presentation and directly proportional to the duration of gestation. The dose in a properly conducted examination is likely to be minute.

A patient with active tuberculosis and positive sputum should be nursed in a sanatorium or chest unit of a general hospital where a visiting obstetrician could be responsible for the ante-natal care. The delivery should be undertaken in an obstetric unit where there are proper facilities for isolation, and where obstetric and pædiatric liaison is available. If the disease is quiescent, the delivery may be at home or in an obstetric unit.

Concerning Breast Feeding. If the mother is non-infective and is anxious to feed her baby, breast feeding may be allowed.

Segregation of Infants. Concerning segregation of infants, the infants should be treated as contacts and given BCG vaccination as soon as possible after birth. If the mother has active disease the infant should be separated from her *immediately*, vaccinated forthwith and segregated until Mantoux conversion has taken place. It may be necessary for relatives or friends to take the infant or he may be admitted to a residential nursery, crêche or children's hospital. Whichever system is adopted, freedom from risk of exposure to any tuberculous person is essential. If the infant is to be boarded out, the inmates of the house where he is sent should all be examined to exclude their having tuberculosis.

If the mother's infection is active and satisfactory segregation is impracticable, the infant should be given isoniazid prophylactically, mg. 3-5/lb./day, and in this event he should be allowed to stay with the mother. As soon as segregation can be arranged this prophylactic therapy should be discontinued, and he should be vaccinated with BCG and only returned when the Mantoux reaction is converted. When an efficient isoniazid-resistant vaccine is generally available, the infant may be vaccinated at birth and isoniazid given concurrently until conversion, and segregation will no longer be necessary. Such a vaccine has been prepared and is undergoing trials.

Copies of the full reports may be obtained from Dr. R. L. Midgley, Hawkmoor Chest Hospital, Bovey Tracey, Devon.

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NOTES AND NOTICES

EDITORIAL BOARD

Dr. John F. Goodwin of the Department of Cardiology at Hammersmith Hospital, is joining the Editorial Board from July next.

WORLD HEALTH ORGANIZATION*

Tuberculosis Death Rate

According to a statistical report of the World Health Organization, there has been a decrease of 50 per cent. or more in the number of deaths from tuberculosis which have taken place in many countries during the period from 1952 to 1957. The World Health Organization is of the opinion that " this drop is mainly a result of the use of new drugs such as Isoniazid and Streptomycin, thanks to which tuberculosis need no longer be a killing disease. Another factor is the intensive tuberculosis case-finding and vaccination campaigns in recent years, as a result of which fewer people contract tuberculosis."

Among the countries and territories covered by the report, the lowest tuberculosis death rate is now found in Iceland, where it dropped from 13·5 per 100,000 population in 1952 to 4·3 in 1957, with a rate of only 2·5 in 1955. The highest rate is in Hong Kong, where it dropped from 158·8 in 1952 to 102·6 in 1957.

In the United Kingdom, the rates per 100,000 in 1952 and 1957 were: in England and Wales 24·1 and 10·6; in Scotland, 31·5 and 14·0; in Northern Ireland 29·8 and 12·5.

THE THORACIC SOCIETY

The Summer Meeting of the Society will take place in Oxford on July 10 and 11.

THE BRITISH TUBERCULOSIS ASSOCIATION

The Thoracic Society of Wales

The Provincial Meeting will be held in Cardiff on April 17 and 18, 1959, and the following subjects are to be included in the programme:

Co-existent Pulmonary Tuberculosis in Bronchial Carcinoma.
Pleural Biopsy.
Surgery in Poor Risk Pulmonary Tuberculosis Patients.
Pneumoconiosis and Carcinoma of the Lung.
Expectorants.
Pulmonary Hydatid Disease.
Pathology of Primary Pulmonary Tuberculosis.
Farmer's Lung.
Caplan's Disease.

ERRATUM

It is regretted that in the paper on " Plasmacytoma of Lung and Stomach," by A. O. Robson and A. Knudsen, in our last issue, the captions to the Figures 7A and 7B were inadvertently transposed.

* WHO Epidemiological and Vital Statistics Report, Vol. 11, No. 10, 1958.

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SOME PERSONAL OBSERVATIONS AND REFLECTIONS ON THE ROLE OF RADIOTHERAPY AND CHEMOTHERAPY AS PRIMARY TREATMENT FOR OAT-CELL CARCINOMA OF THE BRONCHUS

By Elizabeth Kingsley Pillers

From the Department of Radiotherapy, Addenbrooke's Hospital, Cambridge

Introduction

At the present time most physicians and surgeons are dissatisfied with the results of treatment of carcinoma of the bronchus. The present author has been stimulated by this problem, and after experience in chemotherapy in Boston and New York and radiotherapy and radiobiology in Cambridge has had considerable opportunity for thought. In order to try to clarify the problem a study is made of some of the reports of surgical treatment and the factors influencing the survival of patients with this disease. The natural history of bronchial carcinoma and the biological characteristics are discussed, together with some of the newer concepts of how the disease spreads and the more recent attempts to attack the circulating malignant cells. Some of the many reports of treatment by radiation alone or combined with surgery and chemotherapy alone or together with radiotherapy are also investigated. Two patients who came under the author's care at a small Radiotherapy Clinic in a remote part of East Anglia are discussed. Having regard to the limitations of all these methods of treatment it is suggested that chemotherapy together with radiotherapy should be the treatment of choice, even for a patient with an operable lesion, if the histological diagnosis shows an oat-cell lesion or other undifferentiated growth.

Price Thomas (1952) and Holmes Sellors (1955) both reported that only about 20 per cent. of all patients presenting with a diagnosis of carcinoma of the bronchus are suitable for thoracotomy. Approximately 60 per cent. of patients opened were found to have operable lesions and the five-year survival of these patients was 21 per cent. Squamous carcinomata were the most suitable for surgery and made up about 60 per cent. of both series. Price Thomas felt the undifferentiated tumours were often inoperable when first diagnosed, although they occasionally ran a relatively benign course when occurring in an elderly patient. Although the operability is improving with the years and the operative mortality continues to decrease, Sorensen (1956) felt more reserve was needed before embarking on surgery if the patient was over 70 years or if the growth was classified as undifferentiated carcinoma preoperatively. Gifford and Waddington (1957) reported a 30 per cent. five-year survival of all histological types following pneumonectomy, but only 19 per cent. five-year survival of patients with undifferentiated carcinomata. Paulson (1957) had no five-year survivors among about 30 patients following resection for small cell undifferentiated lesions. He stressed the biological

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characteristics in the various types of carcinoma of the bronchus and made a plea for critical selection of patients for surgery, bearing in mind the cell type, the host resistance, the site of the lesion in the lung and the time factor in relation to the natural history of this disease.

The Natural History of Bronchial Carcinoma and Factors affecting Prognosis

In order to assess whether a particular treatment prolonged life, Bignall (1955) and Karnofsky (1957) considered the natural history of bronchial carcinoma. Bignall discusses three groups, 135 patients treated by surgery, 210 patients treated by X-ray therapy and 292 patients who had no specific therapy. He concluded that the duration of life from the start of symptoms depended mainly on the histological type, the duration of illness before diagnosis and the presence of metastases at the time of diagnosis. The highest number of metastases was found in patients with histories of about five months' duration before diagnosis. Karnofsky divided the diseases into three clinical types for retrospective analysis:

Type I: Clinically localised with late generalised disturbances.
Type II: Early generalised disturbances with a short survival time.
Type III: The initial complaint may represent metastases such as liver failure, hypercalcæmia or cerebral symptoms, the primary lesion remaining quiescent.

Charts and suggested methods of record keeping were shown so that patients with a disease showing the same biological characteristics may be selected for evaluation of different forms of treatment.

Many authors have discussed the factors affecting prognosis and survival following treatment, and most of them regard the cell type and mediastinal node involvement as most important. Borrie (1952) found 70 per cent. of nodes invaded with undifferentiated carcinoma as compared with 43 per cent. of node involvement in the epidermoid lesions. Seventy-one per cent. of the patients with undifferentiated lesions were dead in a year, against 31 per cent. of patients with epidermoid carcinoma. Post-operative X-ray treatment to the mediastinum gave no improvement in the survival time of patients with undifferentiated growths, but no post-mortem details were given and it was possible that the local lesion was healed (see Smithers, 1958). The early blood stream spread of this type of disease was emphasised. Bignall and Moon (1955) reiterated many factors mentioned previously (Bignall 1955) in relation to the natural history of bronchial carcinoma. The poorer prognosis of left-sided lung tumours was discussed and thought to be due to the crossed dissemination of the lymphatics from this side. Kirklin (1955) reviewed several other surgical series and reported a 37 per cent. five-year survival following surgery for his own group. In the above study of the relation of cell type to prognosis and treatment, the undifferentiated lesion again showed by far the worst results—findings also confirmed by Kutz (1956). Gibbon (1957) found that survival depended on whether the lesion had spread beyond the lung and reported a

21 per cent. five-year survival following pneumonectomy. Collier (1957) found that blood vessel invasion by the tumour was the most important single factor. In this series 63 per cent. of the squamous carcinoma showed invasion, whereas this was a feature in 100 per cent. of the undifferentiated tumours. The presence of lymph node metastases was found to have little influence on prognosis in the presence of blood vessel invasion. The rapid spread of the oat-celled lesion was confirmed by a series of patients studied by the author of the present paper. In a study of the Bone Marrow in Malignant Disease (Kingsley Pillers, 1956) fourteen bone marrow aspirations showing malignant cells were found in 125 patients with carcinoma of the bronchus. Twelve of these fourteen positive aspirations were found in patients who showed no radiological evidence of metastases and, as a result of recent interest in this subject, it has since been determined that out of the 11 patients with a positive histological diagnosis 7 showed an anaplastic oat-celled lesion. Engell (1955) in a monograph on malignant cells in the circulating blood reminded us that these cells were first observed in 1869, although only in recent years have the identification and diagnosis of these cells been sufficiently certain to enable their full significance to be appreciated. Moore (1957) also identified malignant cells in the blood and found that they disappeared from the circulation after treatment with the anti-tumour agent triethylene thio-phosphoramide (Thio TEPA). Cole (1958) found that the number of malignant cells in the circulating blood increased during surgery and he was also able to destroy the cells with anti-cancer agents. Details of the animal and clinical experiments leading to and arising from these observations are given in two other papers (McDonald, 1957; Morales, 1957) and will be discussed later.

Having reviewed some of the surgical reports and a few other papers which emphasised the biological limitations of surgery in spite of considerable technical advances, the part played by radiotherapy and later chemotherapy can now be discussed.

Radiotherapy Series

Levitt (1955) felt that radical radiotherapy gave disappointing results and was contra-indicated for oat-celled carcinoma or other undifferentiated growths. Bromley (1955) reported on a series of patients treated by radical X-ray therapy followed by resection; out of a group of 732 patients, 66 were eventually found suitable for this combined attack. Five to six weeks' X-ray treatment was followed by a period of convalescence and, after careful evaluation of the patient on clinical, radiological and bronchoscopic examinations, thoracotomy was carried out. At the time of resection a little more fibrous tissue than normal was noted around the hilar structures and post-operatively there was a high incidence of empyema and fistulæ. The post-operative histology showed:

No tumour left—29 cases.
Tumour present but degenerate—14 cases.
Tumour present and viable—19 cases.
Specimens lost—4.
Total: 66.

The final results showed:

10 patients died from operative mortality.
38 patients died from their carcinoma.
5 patients died from unrelated causes.
2 patients were alive with spread of disease.
11 patients were alive and well at the time of the report.

The results according to histology showed the majority of survivors were from the squamous group. It was concluded that this was not a satisfactory method of treatment because of the prolonged treatment and the high incidence of operative mortality and morbidity, even though the survival times ranged from 19 months to $5\frac{1}{2}$ years. This series of patients was reviewed critically by Smithers (1958), who felt that 15 patients with no residual tumour or only degenerate cells present post-operatively had probably been submitted to an unnecessary operation and 6 of these had died because of the operation. Bignall (1956) when studying the effect of X-ray therapy on survival found some increase in survival in the treated group following irradiation, but not enough to make a 10 per cent. improvement in the number of patients surviving 1 year from diagnosis or 5 per cent. in those surviving 2 years. Watson (1956) discussed the value of super voltage roentgen therapy in carcinoma of the lung and reported better survival times than with conventional X-ray therapy; a further improvement in survival times was achieved by using super voltage, together with nitrogen mustard treatment. Smart and Hilton (1956) felt that it was unrealistic to compare the survival rates after surgery or X-ray therapy as the latter patients were all selected as initially unsuitable for surgery. They treated 33 patients, all technically operable and histologically proven, with a seven to eight week course of X-ray therapy. The patients were carefully prepared and treated as in-patients and particular attention was paid to the question of hæmoglobin level, sepsis, diet and adequate sleep, etc. The five-year survival of this small series was 33 per cent., which compared most favourably with any surgical series, especially when it is remembered that usually only 60 per cent. of patients considered " operable " are finally resectable. This is an important series and one of the few that gives an indication of the curative rather than the purely palliative role of radiotherapy. Buschke (1957) felt the undifferentiated carcinomata of the lung behaved clinically like lymphoblastomas and should be treated with X-ray therapy rather than surgery. For other types of carcinoma of the lung surgery remained the method of choice. Shultz (1957) also found a slight though not statistically significant prolongation of life using X-ray therapy for those patients with oat-cell carcinoma. He felt that the unsatisfactory results were due to the early and widespread metastases from this type of lesion, which is essentially very radiosensitive. Wilkins (1957) reviewing the medical progress in carcinoma of the lung considered that the limits of technical advances in surgery have been nearly reached and again mentions super voltage therapy as giving the best palliation for the oat-cell lesions. One of the most significant indications of the value of X-ray therapy alone came from Smithers (1958), who reported

that 7 patients who died after X-ray therapy were found to have no primary tumour at necropsy and 5 of these patients showed undifferentiated lesions histologically. All died from their metastases. Watson (1958) when studying the five-year survivors in a group of over 3,000 patients failed to find any clinical feature distinguishing this group. Among the oat-cell carcinomata although 12 per cent. had resectable lesions only 1 patient survived five years. The figures for X-ray therapy and chemotherapy were equally depressing. It was pointed out, however, that nitrogen mustard gave good palliation if used early in cases of oat-cell carcinoma.

Chemotherapy alone in the treatment of bronchial carcinoma is usually considered to be purely palliative. The value of its use varies from one author to another, but over all the results show room for considerable improvement. McAlpine (1956), Truhaut (1957) and Galton (1958) gave some reports and references to many others. Roswit (1957) reviewed the present status of chemotherapy of bronchial carcinoma and reported good remissions from the use of combined nitrogen mustard and X-ray therapy in the undifferentiated lesion, especially in the syndrome of mediastinal obstruction.

Combined Treatments

The use of combined therapy is by no means new. Two of the earlier reports from the U.S.A. are from Karnofsky (1948) and Roswit (1951). From this country Brooks (1951) reported on the five years' work of the Joint Consultation Clinic for Neoplastic Diseases of the Brompton Hospital and the Royal Cancer Hospital (now the Royal Marsden) and the more recent results from this clinic are reported by Smithers (1958). As already indicated by Galton (1958), the chemotherapeutic agents at present available are too toxic to merit their routine use. Lochman (1956) increased the survival time to 12·8 months by use of X-ray therapy, and nitrogen mustard and X-ray therapy alone gave a 9·4 month average, but this is a small increase considering some of the systemic reactions, due partly perhaps to the high level of dosage of the nitrogen mustard given. By using ACTH together with X-ray and nitrogen mustard, at slightly lower doses, Lorange (1958) avoided severe leucopenia and reported significant palliation. Krabbenhaft (1958) compared the use of combined X-ray treatment and nitrogen mustard for carcinoma of the lung with other methods of therapy and gave the very impressive survival rate of 41·6 months for patients treated with intra-bronchial radium and external irradiation. Closer examination of the figures showed, however, that 2 patients surviving over 280 months and 3 over 125 months accounted for a large part of the high average survival. There was very little difference between the groups treated with X-ray only or X-ray and nitrogen mustard, although only 29 per cent. of the combined group died in the first three months, whereas 38 per cent. of the X-ray group were dead in the same time. It was considered that better palliation of the oat-cell lesions rather than other histological types was achieved with the combined therapy. Mitchell (1953) in an account of the work on cancer of the lung from this department showed that synkavit could be used as a radiosensitiser. There was an increase in survival to ten

months, from the first treatment in the group of patients treated with intravenous synkavit and X-ray therapy, as opposed to five months with X-ray therapy and intramuscular synkavit and 4·4 months with the X-ray therapy alone. The X-ray doses to the tumour were lower than in many other series, but in these patients the disease was too advanced for them to tolerate more than about half of a radical level of X-ray treatment. With the lower dose of X-rays and intravenous synkavit it was possible to demonstrate that a large volume of tissue could be irradiated to a level biologically equivalent to the region of the optimal dose. By this means the therapeutically effective dose was probably increased by about 60 per cent. (Mitchell, 1959). Clinical trials in this field are being continued at Cambridge and one trial has been designed to show whether oxygen at atmospheric pressure will further increase the effectiveness of synkavit as a radiosensitiser (Mitchell, 1957).

Discussion

From the work of Engell (1955), Moore (1957), McDonald (1957), Morales (1957) and Cole (1958) it has been established that malignant cells may be identified in the circulating blood and destroyed by anti-cancer agents. Since Thio TEPA or nitrogen mustard effectively reduced the number of " takes " in rats inoculated with a suspension of cancer cells, W. H. Cole and colleagues decided to try to treat human cancer in a similar way. Nitrogen mustard was given on the day of surgery and for two to four successive days. Even with careful clinical and hæmatological control some increase in post-operative morbidity could not be avoided. Although in this preliminary trial these cases were not patients with carcinoma of the bronchus, there is no reason why this method should not be applicable to patients with this diagnosis. The overall surgical figures for five-year survivals of oat-celled lesions are extremely poor, but several instances of the radio-curability of the local lesion have been given. Two further cases were recently found by the author attending a routine follow-up clinic in a small town in East Anglia. Both patients had lesions in a main bronchus spreading up to the trachea, the bronchial biopsy in each case showed an oat-celled lesion.

Case 1. W.G.L. 61 years. Male.

January 1955. Cough with blood-stained sputum.

July 1955. Pain in right chest with dyspnœa. Chest X-ray showed extensive opacity extending out into the right lung field with the trachea drawn over to the right. Appearances of collapse consistent with a neoplasm. (Fig. 1A.)*

Bronchoscopy. September 1955 showed a carcinoma of the left main bronchus involving the trachea and carinal glands.

September 1955. D.X.R. to anterior and posterior chest using 15 cm. × 15 cm. fields to give a central dose of 1,900 r in eight days (250 kV).

July 1958. Chest X-ray. Considerable clearing of right upper zone with residual collapse and fibrosis. (Fig. 1B.)

April 1959. Apart from very slight dyspnœa on exertion patient remains well and symptom free. Has gained nearly 3 stones since finishing X-ray treatment. Hb. 13·1 g.

* The figure numbers in the text refer to Plate XXIX.

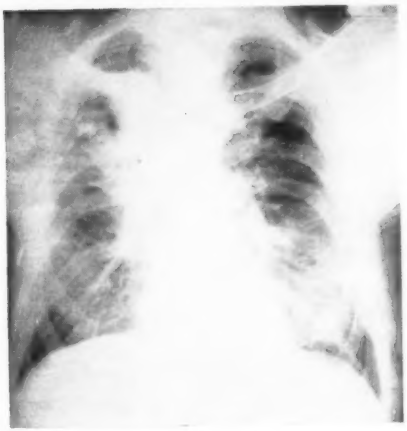

FIG. 1A.—Case 1. W.G.L. X-ray, July 1955, before treatment.

FIG. 1B.—Case 1. W.G.L. X-ray, July 1958.

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CASE 2. J.A.C. 63 years. Male.

January 1952. Cold and cough with brownish sputum.

February 1952. Increasing dyspnœa.

Chest X-ray suggested the presence of carcinoma of the bronchus with a considerable amount of mediastinal involvement.

Bronchoscopy showed a large mass of growth in the right main bronchus extending into the trachea. Patient admitted to Radiotherapy Department at Addenbrooke's Hospital and thought to be in a terminal condition with gross stridor and asphyxia. X-ray therapy was given using 15 cm.+15 cm. fields to deliver 500 r centrally over the anterior and posterior mediastinum. There was immediate improvement and a full course of 2,700 r in fourteen days was given. The patient remained well and symptom free until November 1957, when a large necrotic ulcer developed in the centre of the treated area posteriorly. Since then the patient has been under close observation and no metastases have been demonstrated.

March 1959. The ulcer is granulating slowly and the patient remains entirely free of chest symptoms. He has gained over one stone in weight since completing X-ray treatment. Chest X-ray shows fibrosis of the mediastinum pulling trachea to the right and elevation of hila on both sides. Right upper lobe collapse and fibrosis. No parenchymal metastases. Lumbar spine and pelvis show no bony metastases.

In these two patients the site of the lesion may have been responsible for the diagnosis being established before metastases had occurred. The radiotherapy has apparently controlled the primary lesion as it would seem unlikely, though not impossible, that these two patients will die of metastases.

As a result of this possible radiocurability and the biological characteristics of the disease it is considered that chemotherapy should be used at the time of X-ray therapy for all patients with an oat-cell carcinoma or other undifferentiated growth. The present chemotherapeutic drugs are all extremely toxic and, until a better drug is available, it is suggested that nitrogen mustard is used, giving four daily doses of 0·1 mgm./kilo during the first four days of X-ray treatment, always providing the hæmatological status is satisfactory. The exact level of dosage of X-ray therapy will be decided by the individual radiotherapist, but in view of the high degree of radiosensitivity of this lesion and the hopeless results of radical therapy the lower limit of dosage must be contemplated. By use of synkavit as a radiosensitiser it may be possible to consider the effectiveness of X-ray doses below the optimal level as increased by about 60 per cent. If further trials with a radioactive synkavit establish its therapeutic effectiveness this form of treatment may offer considerable advance in the treatment of carcinoma of the bronchus.

Conclusion and Summary

After consideration of the evidence produced, it is suggested that all oat-cell carcinomata and other undifferentiated growths of the bronchus should be treated by a combination of chemotherapy and radiotherapy. By the use of radiosensitisers, the X-ray dosage can be kept low, which may give a greater margin of safety with the present somewhat toxic chemotherapeutic agents.

I should like to thank Professor J. S. Mitchell, F.R.S., for his helpful discussion of this manuscript.

REFERENCES

BIGNALL, J. R. (1955): *Lancet*, **2,** 210.
(1956): *Lancet*, **1,** 876.
BIGNALL, J. R., and MOON, A. J. (1955): *Thorax*, **10,** 183.
BORRIE, J. (1952): *Ann. roy. Coll. Surg. Eng.*, **10,** 165.
BROMLEY, L. L., and SZUR, L. (1955): *Lancet*, **2,** 937.
BROOKS, W. D. W., DAVIDSON, M., PRICE THOMAS, C., ROBSON, K., and SMITHERS, D. W. (1951): *Thorax*, **6,** 1.
BUSCHKE, F. (1957): *Radiology*, **69,** 489.
COLE, W. H., WATNE, A., ROBERTS, S., and MCGREW, E. (1958): *Proc. 7th Inter. Cancer Congress* —in press.
COLLIER, F. C., BLAKEMORE, W. S., KYLE, R. H., ENTERLINE, H. T., KIRBY, C. K., and JOHNSON, J. (1957): *Ann. Surg.*, **146,** 417.
ENGELL, H. C. (1955): *Acta. chir. scand. Suppl.* 201.
GALTON, D. A. G., and PAPAC, R. (1958): In " Carcinoma of the Lung," chap. xxiii, ed. J. R. Bignall. Edinburgh: Livingstone.
GIBBON, J. H., TEMPLETON, J. Y., and NEALON, T. F. (1957): *Ann. Surg.*, **145,** 637.
GIFFORD, J. H., and WADDINGTON, J. K. B. (1957): *Brit. med. J.*, **1,** 723.
HOLMES SELLORS, T. (1955): *Ibid.*, **1,** 445.
KARNOFSKY, D. A., ABELMANN, W. H., CRAVER, L. F., and BURCHENAL, J. H. (1948): *Cancer (N.Y.)*, **1,** 634.
KARNOFSKY, D.A. (1957): *Radiology*, **64,** 487.
KINGSLEY PILLERS, E. M., MARKS, J. M., and MITCHELL, J. S. (1956): *Brit. J. Cancer*, **10,** 458.
KIRKLIN, J. W., MCDONALD, J. R., CLAGETT, O. T., MOERSH, H. J., and GAGE, R. P. (1955): *Surg. Gynec. Obstet.*, **100,** 429.
KRABBENHAFT, K. L., and LEUCUTIA, T. (1958): *Amer. J. Roentgenol.*, **79,** 491.
KUTZ, E. R. (1956): *J. thorac. Surg.*, **32/2,** 165.
LEVITT, W. M. (1955): *Brit. J. Tuberc. & Dis. Chest*, **49,** 260.
LOCHMAN, D. J., and MORRIS, R. S. (1956): *Radiology*, **66,** 842.
LORANGE, G., METHOT, Y., and TREPANIER, A. (1958): *Un. méd. Can.*, **87/3,** 268.
MCALPINE, S. F. (1956): *Brit. med. J.*, **2,** 1412.
MCDONALD, G. O., LIVINGSTONE, C., BOYLES, C. G., and COLE, W. H. (1957): *Ann. Surg.*, **145,** 624.
MITCHELL, J. S. (1953): *Brit. J. Cancer*, **7,** 313.
(1957): *A.R. Brit. Emp. Cancer Campgn* Part II, 269.
(1959): *Brit. J. Radiol.*, **32,** 214.
MOORE, G. E., SANDBERG, A., and SHUBARG, J. R. (1957): *Ann. Surg.*, **146,** 580.
MORALES, F., BELL, M., MCDONALD, G. O., and COLE, W. H. (1957): *Ibid.*, 588.
PAULSON, D. L. (1957): *Ibid.*, 997.
PRICE THOMAS, C. (1952): *Ann. roy. Coll. Surg. (Eng.)*, **11,** 205.
ROSWITT, B., and KAPLAN, G. (1951): *Radiology*, **57,** 385.
ROSWITT, B. (1957): *Ibid.*, **69,** 499.
SHULTZ, M. (1957): *Radiology*, **69,** 494.
SMART, J., and HILTON, G. (1956): *Lancet*, **1,** 880.
SMITHERS, D. W. (1958): In " Carcinoma of the Lung," chap. xxii, ed. J. R. Bignall. Edinburgh: Livingstone.
SORENSEN, H. R., and THERKELSEN, F. (1956): *Acta. chir. scand.*, **111/3,** 239.
TRUHAUT, R. (1957): *Sem. Hôp. Paris*, **33/62,** 462.
WATSON, T. A. (1956): *Amer. J. Roentgenol.*, **75,** 525.
WATSON, W. L. (1958): *Ibid.*, **79,** 488.
WILKINS, E. E., and SWEET, R. H. (1957): *New Eng. J. Med.*, **256,** 346.

Brit. J. Dis. Chest (1959) **53**, 217.

BRONCHOGENIC CARCINOMA

A MASS RADIOGRAPHY GROUP COMPARED WITH A PRACTITIONERS' GROUP

By James Cuthbert

From the Chest Clinic, S.E. Glasgow

From March 11 to April 12, 1957, an X-ray campaign against tuberculosis was waged in the City of Glasgow. During this period 714,915 persons were X-rayed by 37 units.

Sixty-five persons with suspected malignant conditions within the thorax were seen at the Chest Clinic for the South-eastern part of the City. When secondary neoplasia, Hodgkin's disease, pulmonary fibrosis and malignant mediastinal tumours, etc., were subtracted from this figure forty-eight cases of proven bronchogenic carcinoma remained.

It is the purpose of this paper to compare those Mass Miniature Radiography (M.M.R.) cases with forty-eight consecutive cases of bronchial carcinoma who had been referred to the clinic by general practitioners immediately prior to the Mass Radiography drive. Henceforth the practitioners' cases will be called the " control " group. The comparison of those groups is of topical interest, as lung cancer is on the increase and as it is often stated that mass radiography at regular intervals offers our only hope for its early diagnosis and thus for its effective treatment.

There were, in the control series, 46 males and 2 females. The average age was 58·0 years with a maximum of 79 years and minimum of 34 years.

The M.M.R. group comprised 43 males and 5 females of average age 58·3 years. The oldest patient was 79 years and youngest 39 years. The distribution of the cases in age groups was as follows (Table 1):

Table 1

Age groups in years	30/35	36/40	41/45	46/50	51/55	56/60	61/65	66/70	71/75	76/80	*Totals*
M.M.R.	—	1	2	3	12	15	5	5	3	2	48
Control	1	—	1	4	12	12	10	6	1	1	48

Symptoms

All patients were specifically questioned about symptoms, *i.e.* cough, sputum, pain, hæmoptysis, wheeze, weight loss and dyspnœa, and the duration of those symptoms. Other symptoms were noted. The symptom which was first complained of was the " principal symptom." Other symptoms were called " secondary."

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Table 2 shows the distribution of principal symptoms in the M.M.R. and control series and the average duration in months.

TABLE 2

Principal symptom	*M.M.R.*		*Control*	
	No. of cases	*Average duration in months*	*No. of cases*	*Average duration in months*
Cough	19	2·43	12	2·6
Wheeze	4	1·38	5	1·5
Pain	4	1·0	15	1·42
Hæmoptysis	4	1·38	8	1·34
Weight loss	2	13·0*	0	0
Dyspnœa	2	0·88	6	2·96†
Sputum	1	2·0	0	0
Hoarseness	0	—	1	0·5
Lassitude	0	—	1	3·0
No symptoms	12	—	0	—
Total	48		48	

* One case had noticed weight loss for 2 years.

† One case had dyspnœa for 12 months. The average duration of dyspnœa in the remaining 5 cases was 1·2 months.

Table 3 shows the numbers of instances in which secondary symptoms occurred.

TABLE 3

	M.M.R.	*Control*
	No of instances	*No. of instances*
Cough	4	21
Wheeze	5	16
Pain	8	13
Hæmoptysis	5	12
Weight loss	6	30
Dyspnœa	6	20
Sputum	20	11
Hoarseness	0	0
Lassitude	3	2
Night sweats	0	2
Painful joints	0	3
Headaches	0	0
No secondary symptoms	22	3

The numbers of patients who had secondary symptoms were distributed as follows:

TABLE 4

Numbers of secondary symptoms ..	0	1	2	3	4	5
No. of M.M.R. patients involved ..	22	9	8	5	3	1
No. of control patients involved ..	3	4	10	20	7	4

Diagnosis

Carcinoma is probably the first condition which a clinician thinks of when an adult patient with a radiological abnormality, or symptoms of chest disease, first attends a clinic. Yet it may be a very difficult condition to prove.

The radiological appearances can be sorted into eight broad groups which are listed in Tables 5 and 6 for the M.M.R. and control series respectively. Some films also showed effusions, elevation of the diaphragm, bone erosions, etc., but only the main feature is listed. These tables show the numbers of cases in the X-ray groups, their average numbers of symptoms, those presenting with no symptoms (M.M.R. only) and the length of time taken to diagnose the condition conclusively.

Strong presumptive evidence of lung cancer can be obtained from the history and clinical and radiological examination of the patient. The true diagnosis can, however, only be made by viewing the tumour through a

Table 5

M.M.R.				*Length of time to diagnose*				
				Weeks				
(*a*) *X-ray appearances*	(*b*) *Numbers*	(*c*) *Average No. symptoms*	(*d*) *Nos. of* (*b*) *with no symptoms*	*Under* 1	*Under* 2	*Under* 3	*Under* 4	*Others*
Hilar mass with or without collapse	11	2	2	7 cases	1 case	—	—	4 months* 4 months* 7 weeks
Collapsed lobe or lung with no obvious hilar mass	5	2·4	1	4 cases	1 case	—	—	—
Abscess or cavity alone	1	3	0	—	—	—	—	4 months
Infiltration plus cavity	2	1·5	1	—	—	—	—	5 months 6½ months§
Peripheral mass	9	2	2	7 cases	—	—	1 case	4 months†
Pneumonic like lesion	6	1·7	1	—	—	—	3 cases	1½ months 4 months 5 months
Peripheral, solid rounded focus	10	1·7	3	7 cases	1 case			1½ months 3½ months‡
Lymphangitis carcinomatosa with foci resembling pulmonary tuberculosis	4	2	2	—	—	—	—	5 months 3 months 8 months§ 3 months

* Refused investigation.

† Proven after two bronchoscopies. Unfit for thoracotomy from the start.

‡ Initially a very small focus which suddenly enlarged while patient was under X-ray supervision and patient was then submitted to thoracotomy.

§ Thought at first to be tuberculosis. Initial negative bronchoscopies.

bronchoscope, by finding carcinoma cells in sputum or bronchial washings, by finding the tumour at thoracotomy or post-mortem, or by viewing the progress of the case until secondary growths are proven. The times taken to diagnose the condition in Tables 5 and 6 refer to final diagnosis and not just presumptive diagnosis.

TABLE 6

Control			*Length of time to diagnose in weeks*				
(*a*) *X-ray appearances*	(*b*) *Numbers*	(*c*) *Average No. symptoms*	*Under 1*	*Under 2*	*Under 3*	*Under 4*	*Others*
Hilar mass with or without collapse	22	4	15 cases	4 cases	—	3* cases	
Collapse lobe or lung with no obvious hilar mass	6	4·5	5 cases	1 case	—	—	
Abscess or cavity alone	1	4	—	—	—	—	2 months†
Infiltration plus cavity	0	—	—	—	—	—	
Peripheral mass	8	3·5	5 cases	1 case	2 cases	—	
Pneumonic like lesion	9	3	—	2 cases	4 cases	—	1·5 months 2 months 4 months
Peripheral solid rounded focus	2	2·5	2 cases	—	—	—	
Lymphangitis carcinomatosa plus foci resembling pulmonary tuberculosis	0	—	—	—	—	—	

* Two of those cases refused investigation at first.
† Had antibiotics at first.

TABLE 7

Criteria by which a true diagnosis was first made	*M.M.R.*			*Control*		
	No. of cases	*Later operation*	*Inoperable*	*No. of cases*	*Later operation*	*Inoperable*
X-ray and clinical progress plus metastases	11*	—	11	11	—	11**
Bronchoscopic evidence but no biopsy possible or negative biopsy	10	4	6	19	1	18*
Bronchoscopic evidence with positive biopsy	11	4	7	13	6	7
Proven first at thoracotomy	16†	15	1	5	4	1
* Positive biopsy of a skin node in 4 cases	48	23 (47%)	25	48	11 (23%)	37

† In two instances the specimen was not sent to the laboratory.

Table 7 shows the criteria by which a final diagnosis was first made in each series of cases and whether or not operation was possible. The examination of sputum or bronchial washings for cancer cells was not done as a routine and is not listed.

Table 8 shows the frequency of histological types of tumour where known.

TABLE 8

	Control	*M.M.R.*
Adeno-carcinoma	1	3
Epidermoid carcinoma ..	14	20
Undifferentiated carcinoma..	7	7
Totals	22	30

In Table 9 the criteria by which cases were judged to be inoperable are listed and the numbers of cases in each category from each series.

TABLE 9

Criteria of inoperability	*M.M.R. numbers*	*Control numbers*
Age and/or poor general condition and poor respiratory reserve	6	5
Above and/or bronchoscopic evidence of inoperability	10	18
Distant metastases (includes X-ray evidence of spread)	5	11
Proved inoperable after thoracotomy	1	1
Refused further investigation until too late	3	2
Totals	25	37

Tables 10 and 11 are self-explanatory and show for the M.M.R. and control series respectively the inoperable and operable cases after thoracotomy, the histology of the tumours, the original X-ray appearances and the survival eighteen months after first attending the clinic.

Finally Table 12 shows, for the M.M.R. and control series, the numbers dying each month after first attending the clinic and those surviving after eighteen months. In each series the progress of those cases treated surgically is listed separately.

Discussion

The two series of cases are remarkably similar as regards age distribution. Table 1 shows that the majority of cases in each series are in the period 50 to 65

years. Davidson gives 50 years as an approximate average age and the Department of Health for Scotland's figures for 1951 to 1953 give the peak incidence as 55-64 years.

Taking the 96 cases under review the ratio of males to females was approximately 13 to 1. This is identical with the ratio in 910 patients of Nicholson *et al.*, but higher than the Scottish figures of 10 males to 1 female for 1951-53. Seppala, however, found in 815 cases of lung carcinoma that males comprised 95 per cent., *i.e.* 19 to 1.

TABLE 10.—M.M.R. ANALYSIS OF THORACOTOMIES DONE

	Numbers	*Additional deep X-ray*	*Histology*	*X-ray appearances*	*Survival at 18 months*
Inoperable	1	1	Oat-cell ca.	Hilar mass	Dead 1 year.
1 lobe resected	15	1	Epidermoid ca. 12 cases	7 peripheral round foci 1 peripheral cavity	8 alive at 18 months.
			Adeno-ca. 2 cases	1 segmental collapse 2 peripheral masses	
			No histology done 1 case	3 hilar masses 1 infiltration resembling tuberculosis	7 dead.
Pneumonectomy	6	0	Epidermoid ca. 3 cases	2 peripheral masses 1 hilar mass	2 alive at 18 months.
			Adeno-ca. 1 case	1 collapsed lobe 1 " pneumonic " lesion	
			Undiff. ca. 1 case	1 lymphangitis ca. like tuberculosis	4 dead.
			No histology done, 1 case		
2 lobes resected	2	0	Epidermoid ca. 2 cases	1 peripheral round mass 1 " pneumonia "	2 dead.

TABLE 11.—CONTROL ANALYSIS OF THORACOTOMIES DONE

	Numbers	*Additional deep X-ray*	*Histology*	*X-ray appearances*	*Survival at 18 months*
Inoperable	1	0	Oat-cell ca.	Hilar mass	Dead.
1 lobe resected	2	0	Epidermoid ca. 2 cases	Peripheral mass Peripheral round shadow	2 alive.
Pneumonectomy	7	0	Epidermoid ca. 6 cases	Hilar mass, 3 cases " Pneumonia," 1 case	3 dead.
			Adeno-ca. 1 case	Peripheral mass, 2 cases Collapsed lobe, 1 case	4 alive.
2 lobes resected	2	0	Epidermoid ca. 2 cases	" Pneumonia," 1 case Collapsed lobe, 1 case	2 dead.

TABLE 12

Months:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	*Surviving over 18 months*	
Nos. of M.M.R. series dying	1	4	2	3	2	3	4	2	3	2	4	1	1	–	1	1	1	–	13	Total 48.
Surgical cases from M.M.R. series	*1	3	–	–	–	–	1	1	1	2	–	–	–	1	1	1	–		11	Total 23.
Nos. of control series dying	7	4	10	8	1	4	–	2	1	–	1	–	2	–	–	–	–	–	8	Total 48.
Surgical cases from control series	–	1	1	2	–	–	–	1	–	–	–	–	–	–	–	–	–	–	6	Total 11.

* Coronary thrombosis death.

Symptoms

There are two significant features in the symptomatology (Tables 2 and 3). Only 12 of the M.M.R. group had no symptoms and this is supposed to be a symptom-free group. Proper history taking shows that in fact 36 persons discovered by M.M.R. had one or more of the cardinal symptoms of chest illness, and when the principal symptoms only, in the two series, are compared there is no great difference in the length of time that the symptoms had been present in each series.

However, Tables 3 and 4 show that there were more secondary symptoms on the average in the cases sent to the clinic by practitioners and that 22 of 48 M.M.R. cases had no secondary symptoms at all.

We can only speculate why 36 persons in the M.M.R. group had symptoms. They may have intended to consult their practitioners but took advantage of the M.M.R. drive. Garland and Johnson state that many patients attend mass surveys because they have symptoms.

On the other hand, I am inclined to think that bronchitis and coughing from cigarette smoking is so common that most people tend to ignore chest symptoms unless something startling, such as hæmoptysis, occurs. Even then some persons do not consult their doctors, and in the M.M.R. and control series 4 and 8 patients gave hæmoptysis as a principal symptom, noted on an average 1·38 and 1·34 months previously.

It appears that much more propaganda is required to teach the public to be X-ray conscious when they have chest symptoms.

Considerations in diagnosis

Tables 5 and 6 show that in each series the cases were fairly equally distributed into the eight radiological patterns which I have chosen.

The 12 M.M.R. cases who had no symptoms were not confined to one particular X-ray group but were distributed throughout.

On the whole the cases who were sent up by practitioners took less time to diagnose conclusively than the M.M.R. cases. Indeed the whole study shows that they were more advanced.

The cases in which diagnosis is delayed are chiefly those presenting as pneumonia. Although carcinoma is usually suspected from the first, infection has often to be controlled with antibiotic therapy before the patient is fit for bronchoscopy. Shields *et al.* (1957) stress the difficulty in diagnosis where pneumonias in the elderly resolve slowly. Similarly, some peripheral cavities with surrounding inflammation or cases with localised lymphangitis carcinomatosa can resemble pulmonary tuberculosis and give no evidence of their true nature on initial bronchoscopy.

The majority of cases of uncomplicated carcinoma which are within bronchoscopic vision can be diagnosed in 24 hours by bronchoscopy at the clinic. Greenberg (1956) states that in 33 cases of mass survey detected lung cancer, only 36·4 per cent. were diagnosed within 1 month after X-ray.

In the main only those who were judged to be operable were admitted to hospital for further assessment. The rest were treated initially at home. This explains why the histological types were known in only 22 and 30 instances in the control and M.M.R. groups respectively (Table 8).

In only a few instances was a search made for cancer cells in the sputum, so that this aspect of diagnosis does not apply to the two series.

Epidermoid carcinoma predominated and undifferentiated carcinoma came next in frequency (Table 8) as is found in most other series, *e.g.* Walter and Pryce (1955) in 207 resected lung cases found squamous cell carcinoma in 60·4 per cent., oat-cell carcinoma in 15·9 per cent., polygonal cell carcinoma in 7·7 per cent., adenocarcinoma in 15·5 per cent. and malignant " adenoma " in 0·5 per cent.

Livingstone's figures (1957) show squamous carcinoma in 45 per cent., anaplastic or oat-celled carcinoma in 35 per cent., peripheral (often adenocarcinomata) 20 per cent. and alveolar celled carcinoma ½ per cent.

Paulson (1957) in 444 proven cases found 64 per cent. squamous, 20 per cent. undifferentiated and 16 per cent. adenocarcinomata.

The histology was known of 5 of the 7 female cases in our total series: 2 were epidermoid and 3 undifferentiated carcinomas. It is significant that no adenocarcinoma was proven.

Treatment

We still think of treatment of lung cancer in terms of surgical extirpation. Table 9 shows that approximately 50 per cent. of the M.M.R. series and only 23 per cent. of the practitioners' group were deemed suitable for surgery. Tables 10 and 11 are self-explanatory.

In the Scottish figures for 1951 to 1953 in the Eastern and North-eastern regions, less than 20 per cent. were considered fit for radical surgery.

Bishop (1957) found 20 per cent. of 100 cases to be inoperable on thoracotomy and only 21 per cent. were resected.

In each of our series a very significant feature is that the cases who have survived over eighteen months are practically all cases who were treated by surgery. Only two patients in each group survived for 18 months without surgery.

In those operation cases surviving over 18 months it will be seen that

cases who had one lobe removed fared as well or as badly as those having pneumonectomy (Tables 10 and 11).

Those findings are similar to those of Overholt (1956) *et al.* discussing 101 three-year survivors.

It would appear that in order to get cases of carcinoma early enough to be treated, one would have to X-ray persons in the cancer age group every six months approximately, and this is not a practical proposition.

Summary

Forty-eight cases of bronchogenic carcinoma seen at one clinic in Glasgow after the City-wide Mass Radiography survey are compared with 48 consecutive cases sent with symptoms to the clinic by practitioners.

Only 12 of the M.M.R. group had no symptoms, and it is concluded that more propaganda is necessary to make the public X-ray conscious as regards chest symptoms.

Difficulties of diagnosis arose with those cases which presented as pneumonia, peripheral abscess, or with lymphangitis carcinomatosa, resembling tuberculosis on the X-ray, and with negative bronchoscopic findings.

On the whole the M.M.R. group fared better than the practitioners' group, and at eighteen months from first attending the clinic 13 of them were alive, compared with 8 in the practitioners' group.

Operation, be it removal of one lobe or pneumonectomy, offers the best hope of survival to eighteen months.

My thanks are due to Mr. R. S. Barclay and the members of the thoracic surgical unit at Mearnskirk Hospital for their help with the cases admitted to that unit.

REFERENCES

Bishop, C. A. (1957): *J. thorac. Surg.*, **33**, 330.
Davidson, M. (1954): " Practical Manual of Diseases of the Chest," 4th Edn. London: Oxford Medical Publications.
Health Bulletin, Dept. of Health for Scotland, 1957, **15**, 5.
Garland, L. H., and Johnson, J. (1957): *Postgrad. Med.*, **22**, 417.
Greenberg, R. A. (1956): *Conn. med. J.*, **20**, 857.
Livingstone, J. L. (1957): *Brit. J. clin. Practice*, **11**, 831.
Nicholson, W. F., Fox, M., and Bryce, A. G. (1957): *Lancet*, **1**, 296.
Overholt, R. H., and Bougas, J. A. (1956): *J. thorac. Surg.*, **32**, 508.
Paulson, D. L. (1957): *Ann. Surg.*, **146**, 997.
Seppala, A. J. (1958): *Acta oto-laryng. (Stockh.)*, **49**, 81. Quoted *Tub. Index*. Sept. 1958.
Shields, D. O., Meador, R. S., Du Bose, H. M., and Richburg, P. L. (1957): *Amer. Rev. Tuberc.*, **76**, 47.
Walter, J. B., and Pryce, D. M. (1955): *Thorax*, **10**, 107.

Brit. J. Dis. Chest (1959) **53**, 226.

INTERSTITIAL PNEUMONIA AND ITS CONSEQUENCES IN RHEUMATOID DISEASE

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Several lung lesions have been described in patients suffering from rheumatoid disease, viz.,

1. rheumatoid granulomata (Raven *et al.*, 1948),
2. rheumatoid pneumoconiosis, or Caplan's syndrome (Gough *et al.*, 1955),
3. necrotising arteritis (Könn, 1956),
4. sclerosis of pulmonary arteries (Gardner *et al.*, 1957),
5. focal arteritis, bronchiolitis and interstitial pulmonary fibrosis (Price and Skelton, 1956),
6. interstitial pneumonitis (Ellman and Ball, 1948),
7. diffuse interstitial pulmonary fibrosis (Rubin, 1955), and
8. honeycomb lung (Dixon and Ball, 1957).

The occurrence of most of these lesions has been confirmed by several authors since the first descriptions. The rheumatoid nature of the first two lesions is not questioned; Könn's case is probably an example of severe rheumatoid arteritis (Ball, 1954; Cruickshank, 1954); the case described by Gardner *et al.* showed concurrent pulmonary hypertension and rheumatoid disease.

The significance of the remaining lesions has been interpreted in different ways. Aronoff *et al.* (1955) regarded them as unrelated to the rheumatoid disease. They found no specific lesions in 253 patients, but it is not clear how often histological examination was made in that series. One example of honeycomb lung encountered by these authors was interpreted as idiopathic. Ellman and Ball (1948) and several subsequent authors, who have examined the lesions histologically (Rubin, 1955; Price and Skelton, 1956; Edge and Rickards, 1957), have regarded the various lesions as pulmonary manifestations of rheumatoid disease, though none of these authors has claimed that the pathological changes in the lungs were specific. There is thus a need for further work to assess the ætiological significance and the pathogenesis of these non-specific lesions.

The object of the present report is to record eight further examples of interstitial pneumonia, pulmonary fibrosis or honeycomb lung associated with rheumatoid disease and to assess the ætiology and pathogenesis of these changes. Five of the cases have been observed personally: full autopsies were performed on these patients, numerous blocks were taken from the lungs and other tissues and sections from these have been stained by various methods. Sections and clinical notes from the others have been made available by Professor J. Gough

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(Cases 1 and 7) and Dr. H. Spencer (Case 8). These eight cases have been classified according to the diagnostic criteria of Ropes *et al.* (1958). In addition material from three cases reported previously has been available for study (Hart and Mackenzie, 1955; Ellman, 1956, Case H.L.; Dixon and Ball, 1957).

Case Abstracts and Pathological Findings

Case 1. Female, aged 56 at death. Onset of rheumatoid type of arthritis fourteen years earlier, involving hands, wrists, shoulders and knees. Subcutaneous nodules on both forearms. No evidence of respiratory disease. Developed femoral vein thrombosis, followed by sudden severe dyspnœa and chest pain, and died the next day.

At autopsy there was slight fibrinous pleurisy over the left lower lobe. Detailed examination of the expanded lung revealed some small pale foci in all lobes.

Histologically many small arteries, arterioles and bronchioles were surrounded by a thick cuff of lymphocytes with smaller numbers of plasma cells and macrophages (Fig. 1).* This infiltration had spread into the walls of adjacent alveoli. No fibrosis was seen, nor was there any dilatation of the air passages. A few dust cells were present in the alveoli, but there was no evidence of an intra-alveolar inflammatory exudate.

Other findings were thrombosis of the veins of the left leg and pulmonary embolism. The synovial changes were characteristic of rheumatoid arthritis and a nodule from the elbow region was a rheumatoid granuloma.

Comment: Classical rheumatoid disease, with foci of interstitial pneumonia.

Case 2. Male, aged 58 at death. Joint pains intermittently since the late teens, commencing in right foot and ankle; left foot, both wrists and fingers successively involved. Clinical features typical of rheumatoid arthritis. Developed acute respiratory illness with cough, fever, dyspnœa and pleurisy in 1956; X-ray of chest at this time showed fine reticular shadows in both mid- and lower zones and in left upper zone (Fig 2A). Several similar episodes thereafter. X-ray of chest on 19.8.57 showed considerable progression of the changes (Fig. 2B). At final admission on 23.5.58 clinical and radiographic examination confirmed late rheumatoid arthritis. Subcutaneous nodules present on both forearms. Diminished air entry at right base, scattered rhonchi throughout, bronchial breathing at left base and bilateral basal crepitations. Culture of sputum for tubercle bacilli negative. Vomiting had commenced three weeks before admission and continued until death on 1.6.58. Liver and spleen had become palpable, there was marked albuminuria, hyperglobulinæmia and uræmia.

At autopsy scattered fibrous adhesions were observed in both pleural cavities. Both lungs were congested, with chronic bronchitis and emphysema and a large patch of confluent bronchopneumonia in the left upper lobe. Scattered through all lobes were numerous small nodules up to 1 cm. in diameter, apparently related to bronchioles. They were most numerous in the subpleural regions.

Histologically the nodules were centred around bronchioles and showed interstitial pneumonia with many lymphocytes and plasma cells, often in dense foci, and well-marked rather loose collagenous fibrosis. Tiny granulomata were

* The figure numbers in the text refer to Plates XXX-XXXIII.

present in many of the foci (Figs. 3 and 4) and consisted of a central degenerate zone, infiltrated with polymorphs and surrounded by large macrophages or undifferentiated mesenchymal cells often arranged radially. Occasional multinucleated cells were seen. Acute bronchiolitis was seen in some of the foci. Arteries and arterioles showed marked fibrosis and elastic reduplication (Fig. 5); destruction of a segment of the wall was occasionally seen. The largest nodules showed diffuse fibrosis involving irregular portions of lung and sometimes incorporating the lesions already described. Some bronchioles in these larger foci were collapsed. Neither tubercle bacilli nor crystalline material could be demonstrated in the granulomata.

Other findings were secondary amyloidosis involving kidneys, spleen, adrenals, thyroid and liver. The joint lesions were characteristic of rheumatoid arthritis and the subcutaneous nodule was a rheumatoid granuloma.

Comment: Classical rheumatoid disease, with foci of interstitial pneumonia and fibrosis, including minute rheumatoid granulomata, fibrosis and occasional destruction of small arteries.

CASE 3. Female, aged 72 at death. Onset of rheumatoid type of arthritis nine years before death, involving hands, wrists, elbows, ankles and knees. No respiratory symptoms. Admitted a month before death with clinical features suggestive of a myocardial infarct. X-ray of chest at this time showed a coarse reticular pattern in the lower zones. Deteriorated gradually until death.

At autopsy there were scattered pleural adhesions. The lungs showed moderate chronic venous congestion, particularly in the lower lobes. These were unusually firm, but not consolidated, and showed widespread mild to moderate emphysema.

Histologically there was well-marked and widespread fibrosis in the lower lobes (Fig. 6). This had obliterated the normal architecture in places and was elsewhere associated with bunching together of dilated bronchioles, alveoli and occasional bronchi. Patchy infiltration with lymphocytes and plasma cells was seen in the fibrous tissue. Occasionally the air spaces contained œdema fluid, sometimes with a few polymorphs, but these changes were not marked. Small and medium-sized arteries showed marked fibrosis, sometimes with reduplication of the elastic tissue.

Other findings were pericardial fibrosis, hypertrophy of the left atrium and ventricle, subacute myocarditis and fibrosis of the mitral and aortic valves. No evidence of a myocardial infarct was found.

Comment: Definite rheumatoid disease, with interstitial fibrosis, patchy bronchiolectasis and fibrosis of small arteries.

CASE 4. Male, aged 73 at death. Onset of rheumatoid type of arthritis seven years before, involving hands, wrists and knees. Admitted to hospital four years before death with breathlessness on exertion and œdema of feet and ankles. No previous history of cardiac or respiratory disease. No cause for cardiac failure found. Remained in hospital, deteriorating slowly, until death.

At autopsy there were chronic adhesions in both pleural cavities and an organising fibrinous exudate on the right side. Both lungs were œdematous, with patchy subpleural fibrosis associated with small cysts. No evidence of old or recent bronchitis was seen, nor was there any consolidation.

Histologically the pleura was thickened in relation to the cystic regions. The cystic spaces were lined by a single layer of flattened or cuboidal epithelium,

with plain muscle but no cartilage in the underlying tissues (Fig. 7). Marked old-standing fibrosis was seen in the interstitial tissue, distorting the normal architecture and producing thick septa between the cysts. Occasional foci of ossification were seen in these septa. Dense foci of lymphocytes and plasma cells were scattered through the interstitial tissue, sometimes impinging on and partially surrounding the dilated bronchioles. Considerable fibrosis was present in the small arteries.

Other findings were chronic venous congestion of liver, spleen and kidneys. The knees showed old-standing inactive arthritis of rheumatoid type.

Comment: Definite rheumatoid disease, with focal interstitial fibrosis, bronchiolectasis and fibrosis of small arteries.

CASE 5. Male, aged 57 at death. Rheumatoid type of arthritis commenced four years before death and involved hands, wrists, shoulders, ankles and knees. Attack of dry pleurisy thirty years previously but no respiratory disease in the interval. Attack of pleurisy on left side one year before. Admitted one month before death with dyspnœa, epigastric pain and vomiting. Found to have right-sided pleural effusion which was purulent on aspiration; a mixed culture was obtained, with Friedländer's bacillus predominating. ECG evidence of myocardial infarct. Further aspiration of 11 pints of purulent pleural fluid, rapid deterioration and death.

At autopsy the right-sided empyema was confirmed and the left pleural cavity was considerably reduced by fibrous adhesions. The lungs were greyish-pink and the left lung had a finely granular feel with emphysematous spaces up to 5 mm. in diameter beneath the pleura. The right upper lobe was collapsed and the middle and lower lobes were the site of confluent bronchopneumonia.

Histologically in the left lung there was old fibrosis of the pleura but no recent inflammation. The " emphysematous " spaces were lined by a single layer of epithelium, which varied from flattened to low columnar. Plain muscle was present in the walls of most, but no cartilage was seen. These dilated bronchioles were separated from one another by thick septa showing considerable established fibrosis and extensive infiltration with lymphocytes and plasma cells in varying proportions. Occasionally the tissue had a granulomatous appearance, with proliferating fibroblasts in addition to the inflammatory cells (Fig. 8). Numerous congested capillaries were present throughout the septa. Arteries showed marked intimal and medial fibrosis and elastic reduplication.

Other findings were thrombosis of the left coronary artery with myocardial infarct; healed renal infarct; chronic cholecystitis; subacute mitral valvulitis; inactive rheumatoid type of arthritis in knees.

Comment: Definite rheumatoid disease, with focal interstitial fibrosis, bronchiolectasis and fibrosis of small arteries.

CASE 6. Female, aged 54 at death. Typical rheumatoid type of arthritis began at age of 50, affecting hands, wrists, shoulders and knees. Dyspnœa and cough began at the same time. Radiographs suggested bronchiectasis. Bronchoscopy and bronchography twelve days before death, followed by slight pyrexia for a few days. Admitted five days before death with fever, cyanosis, severe dyspnœa and clinical signs of bilateral bronchopneumonia. Became more dyspnœic despite vigorous chemotherapy and continuous oxygen and died.

At autopsy the pleural sacs were healthy, although the interlobar fissures

on the right side were obliterated. Numerous cysts, up to 1 cm. in diameter, projected from the pleural surfaces of all lobes. They were most numerous and closely set along the anterior border. On the cut surfaces the cysts were seen throughout the lung tissue and were surrounded by thin fibrous septa. Some of the cysts communicated with bronchi. More marked fibrosis accompanied the cysts in the left upper lobe. Considerable portions of lung tissue were non-cystic, particularly in this lobe. Numerous ill-defined, firm, hæmorrhagic lesions were present in such regions.

Histologically (Fig. 9) many of the cysts were lined by columnar ciliated epithelium with a variable amount of plain muscle, but no cartilage, in the lamina propria. Other cysts had no epithelial lining or muscle in their walls. Globules of fatty material were dispersed through the air spaces associated with polymorphs, mucus and varying numbers of macrophages, some of which had absorbed the lipid. Heavy interstitial infiltration with plasma cells and lymphocytes were seen in the walls of many of the cysts. Some of the spaces were lined with several layers of macrophages which merged with the surrounding inflammation, giving a granulomatous appearance (Fig. 10). Interstitial fibrosis was present in many places but was less marked than in the other cases. Very many dilated and congested capillaries were present in the interstitial tissue. Most of the smaller arteries showed intimal fibrosis which was often sufficiently severe to cause marked narrowing of the lumen. The various pathological changes in the interstitial tissue tailed off gradually into regions where the lung tissue had a more normal appearance, but even here the alveoli frequently showed emphysema. Organisation within alveoli was occasionally seen in such regions but affected only small foci and was obviously a very minor feature. Occasional more solid regions were seen in which dense interstitial fibrosis had all but obliterated the lung architecture. Such regions contained a few dilated bronchioles and there was patchy inflammation similar to that already described, including the granulomatous reaction. The ill-defined hæmorrhagic lesions showed recent intra-alveolar exudation of fibrin, erythrocytes and polymorphs, associated with œdema and congestion of the alveolar walls.

The joint lesions were those of inactive rheumatoid arthritis. The only other finding was mild non-specific myocarditis.

Comment: Definite rheumatoid disease, with honeycomb lungs, interstitial pneumonia, interstitial fibrosis and fibrosis of small arteries.

Case 7. Female, aged 69 at death. Developed rheumatoid type of arthritis ten years before death, involving hands, wrists, elbows, shoulders, ankles and knees, resulting in gross damage to hands and knees. Subcutaneous nodules developed on both forearms. Developed pain and tightness in right side of chest two months before death, with fever, cough and expectoration of thick sputum; flare-up of arthritis coincided with these features. Respiratory disease responded to penicillin. Cortisone had no effect on the arthritis. Developed acute urinary infection and died.

At autopsy there were extensive bilateral pleural adhesions. Hard nodules were palpable throughout the lungs, particularly in the upper lobes. A cystic appearance was seen on the pleural surface, particularly in the left upper lobe. On section there was diffuse fibrosis, with patchy honeycomb lung.

Histologically the cystic spaces were mostly of bronchiolar origin, though

cartilage was present in a few. The lining epithelium varied from a single flattened layer to several layers of columnar cells. There was much old-standing fibrosis between the spaces, forming septa up to 1 mm. thick, in which there was patchy mild to moderate infiltration with lymphocytes and plasma cells. Considerable intimal fibrosis was seen in small arteries. In the more solid regions interstitial fibrosis was very marked, causing complete disorganisation of the lung architecture. Distended bronchioles were present and sometimes showed quite marked epithelial proliferation, with a small carcinoma in one region. The other features noted in the cystic regions were again present and there was patchy acute inflammation centred around some of the bronchioles. Foci of interstitial pneumonia, similar to those in Case 1, were seen even in the more normal portions of the lungs, associated with vesicular emphysema.

Other findings were multiple ulcers of the œsophagus; pyelonephritis with renal medullary necrosis. The appearances in the right knee and a metacarpophalangeal joint were characteristic of rheumatoid arthritis; acute suppurative changes were present in the left knee and sternoclavicular joint, from both of which *Staphylococcus aureus* was isolated. The subcutaneous nodules were rheumatoid granulomata.

Case 8. Male, aged 65 at death. Onset of typical rheumatoid type of arthritis nine years before death, affecting most of the small joints, but principally the hands and feet. Subcutaneous nodules present on right forearm. Breathlessness on exertion throughout the illness. Shortly before the final admission the breathlessness became worse and there was cyanosis on exertion. Clubbing of the fingers had developed. The patient died suddenly, shortly after admission.

At autopsy the pleural surfaces were thickened, although there were no adhesions. The subpleural zones of the lower lobes were fibrosed and replaced by a honeycomb of cysts, some of which were continuous with bronchi.

Histologically the striking feature was the presence of numerous dense foci of lymphocytes, often with a germinal centre, in the thick septa, which were often 1 mm. thick (Fig. 11). The cysts themselves had often lost their epithelial lining, which could be seen lying in the lumen; where present the epithelial cells were cuboidal or columnar. No cartilage was seen in the septa but plain muscle was present among the fibrous tissue and lymphoid follicles. Many congested capillaries were seen in the septa and the small arteries showed considerable fibrosis and reduplication of the elastic laminæ, resulting in marked reduction in the size of the lumen. Many of the cysts contained considerable numbers of dust cells and in a few there was also a muco-purulent exudate. The cystic zone, which was 1-1·5 cm. broad, tailed off gradually into normal lung tissue.

Other findings were thrombosis of the left coronary artery.

Comment: Classical rheumatoid disease, with interstitial pneumonia, patchy honeycomb lung and fibrosis of small arteries.

Discussion

Although the pathological changes vary somewhat from case to case, certain features are common to most or all of them. These include the interstitial situation of the significant lesions, the non-specific nature of the inflammation and the fibrosis associated with bronchiolectasis. It is noteworthy that the only significant evidence of an exudate within the air-containing tissue is an acute,

and presumably terminal, bronchitis or bronchopneumonia. The cellular elements of the interstitial pneumonia are similar to those which occur in the synovial tissue and other inflammatory lesions of rheumatoid disease. Furthermore there is a tendency to the formation of definite nodules of such cells, sometimes with germinal follicles (Cases 4 and 8). These features have all been noted in previously recorded cases in which histological examination was made (Ellman and Ball, 1948; Rubin, 1955; Ellman, 1956; Edge and Rickards, 1957; Rubin and Lubliner, 1957). The appearances in the three previously recorded cases from which sections were available for study show no essential difference from the others in the present series. The focal lesions in Case 2 are similar to those described by Price and Skelton, with the additional feature of the small granulomata.

Examination of the previous reports and of the material now available makes it possible to suggest a definite sequence of events. The earliest change, in the majority of cases, is a non-specific interstitial pneumonia (Case 1; Ellman, 1956, Case H.L.). At this stage the process is reversible and resolution probably occurs in many patients. If the inflammation persists, fibrosis also occurs and becomes increasingly prominent. A definite antecedent lesion responsible for the fibrosis was seen in Case 2, namely the small foci which had many of the features of the rheumatoid granulomata characteristic of the disease. Although destructive changes had occurred in some small arteries in this patient's lungs there was no evidence of arteritis elsewhere and the granulomata were not like those described in the pulmonary lesions of polyarteritis nodosa (Rose and Spencer, 1957). Granulomatous changes were also seen in Cases 5 and 6, but the lesions were not characteristic. Those in Case 6 were similar to the changes described by Cunningham and Parkinson (1950) in a series of cases of honeycomb lung. There is no evidence from the present cases that organisation of intra-alveolar exudate plays any part in the development of the interstitial fibrosis (Heppleston, 1951), and Lodge (1956) has noted that respiratory infections are not associated with progression of the fibrosis as seen in radiographs. Nevertheless, once fibrosis has become established, the subsequent development of bronchiolectasis (Cases 3, 4, 5), with honeycomb lung as its extreme form (Cases 7 and 8; Hart and Mackenzie, 1955; Dixon and Ball, 1957), probably follows the pattern outlined by Heppleston (1956). Ellman and Cudkowicz (1954) have suggested that the lung lesions in rheumatoid disease and in other chronic rheumatic diseases develop on the basis of ischæmia following damage to the bronchial arteries. It is impossible to decide whether the vascular lesions encountered in the present study involved branches of the bronchial or pulmonary arteries or both. They are most satisfactorily interpreted as secondary to the interstitial pneumonia and fibrosis, but they occurred so constantly and were sometimes so severe as to suggest that ischæmia may have been a secondary factor in causing permanent damage.

It is interesting to consider the relationship between the changes described here and other lesions which are known to occur in the lungs of patients with rheumatoid disease, in particular with those of Caplan's syndrome. Five of the present cases were drawn from a series of 100 autopsies (Cruickshank, 1957).

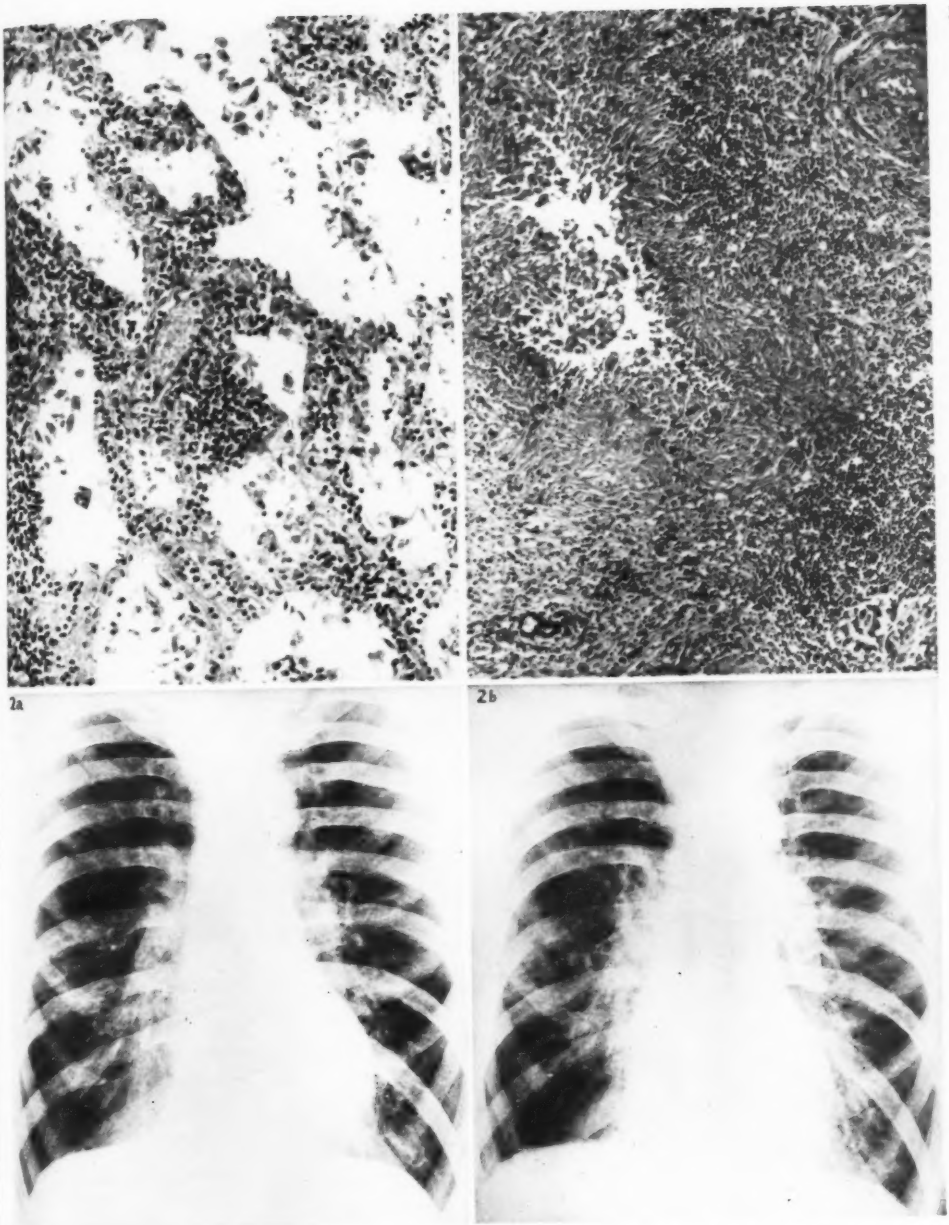

FIG. 1.—Case 1. Cellular interstitial pneumonia, with infiltration of lymphocytes around a bronchiole (left) and vein and in adjacent septal walls. Haematoxylin and eosin. (H. and E.; ×150.)

FIG. 3.—Case 2. Focus of diffuse interstitial pneumonia with small granulomatous lesion. Marked thickening of wall of small artery (top right). (H. and E.; ×85.)

FIG. 2.—Case 2. Radiographs of chest taken (a) 2 years and (b) 1 year before death. Note the progressive fine reticular shadows in the mid- and lower-zones.

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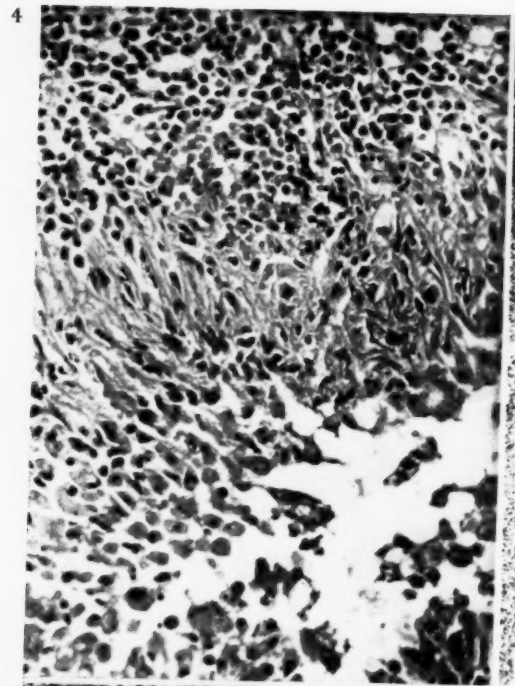
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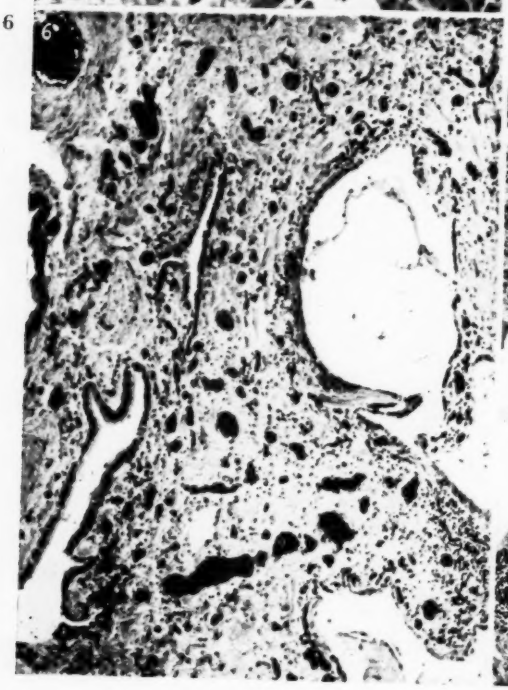
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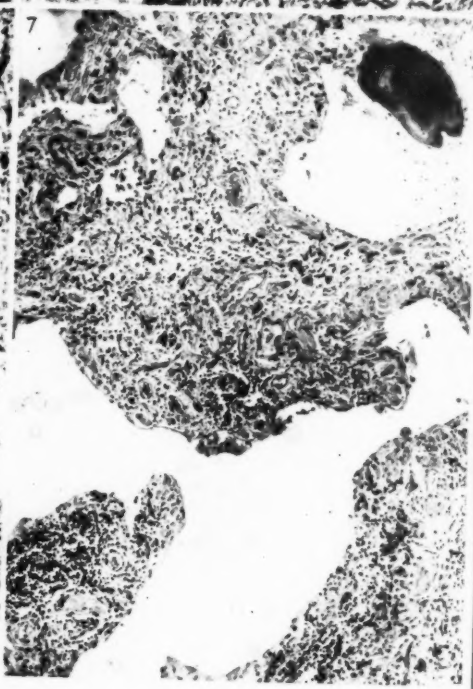
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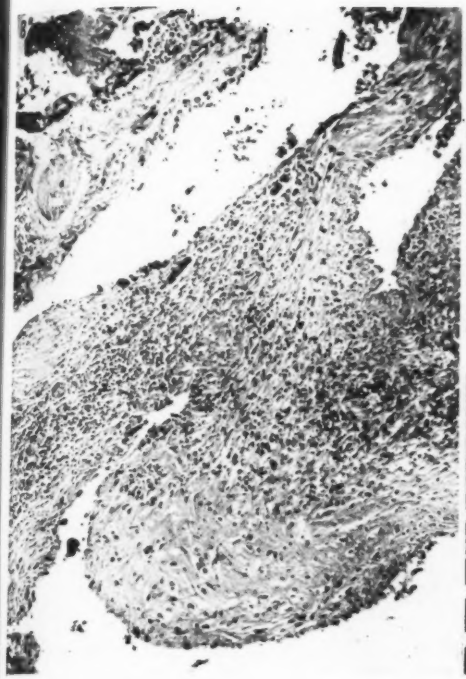

FIG. 8.—Case 5. Granulomatous lesion in large septum between two dilated bronchioles. (H. and E.; ×65.)

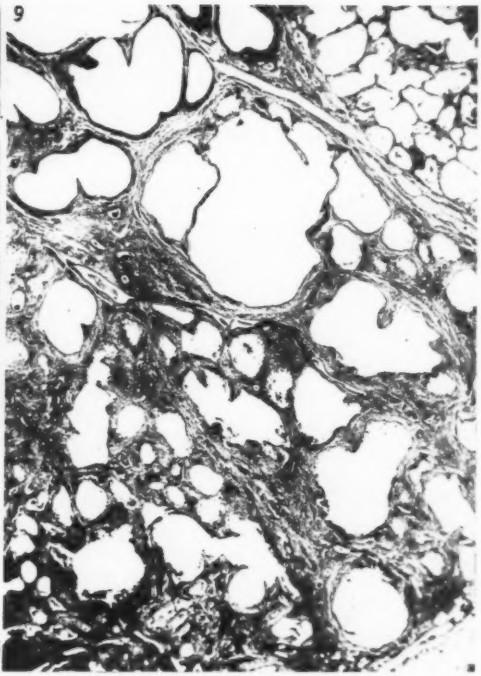

FIG. 9.—Case 6. Numerous dilated bronchioles separated by fibrous septa containing inflammatory foci. Dilated alveoli are also seen (top right). (H. and E.; ×15.)

Opposite

FIG. 4.—Case 2. Detail of the granuloma in Fig. 3. The central space is surrounded by large macrophages and undifferentiated mesenchymal cells, with an outer zone of lymphocytes and plasma cells. (H. and E;. ×265.)

FIG. 5.—Case 2. Part of largest focus, showing much fibrosis involving interstitial tissue and a small artery (top right). Foci of lymphocytes (left). (Elastic-van Gieson. ×80.)

FIG. 6.—Case 3. Several dilated bronchioles surrounded by dense fibrous tissue containing many congested capillaries. (H. and E.; ×100.)

FIG. 7.—Case 4. Dense interstitial fibrosis and patchy cellular infiltration around dilated bronchioles. Spicule of bone (top right). (H. and E.; ×65.)

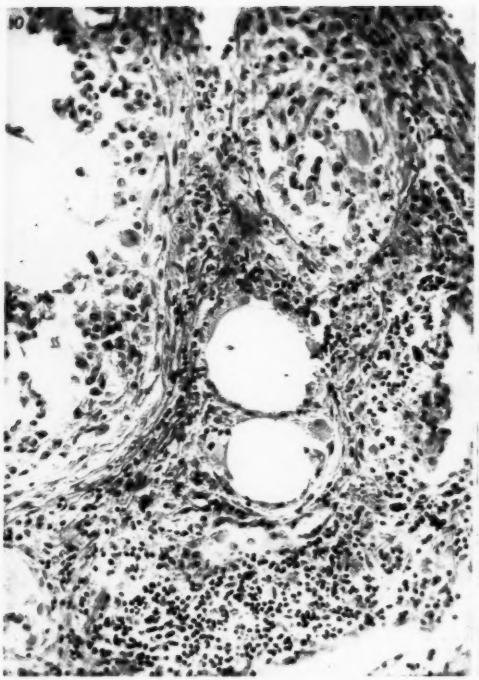

FIG. 10.—Case 6. Detail of granulomatous reaction around one large cyst and in adjoining septum. (H. and E.; ×150.)

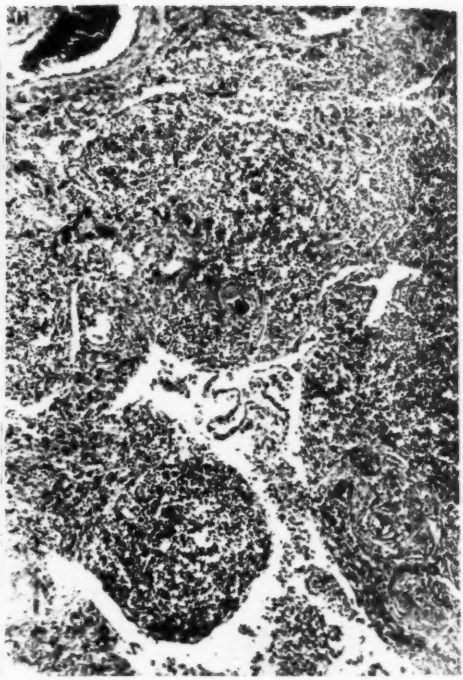

FIG. 11.—Case 8. Massive infiltration with lymphocytes around a dilated bronchiole. A germinal centre is seen (bottom left) and a small artery (bottom right) shows marked fibrosis. (H. and E.; ×65.)

No examples of Caplan's syndrome were encountered in that series and Case 2 was the only example of rheumatoid granulomata. Pulmonary fibrosis was seen in sixteen patients other than those described here. Eleven of these were examples of active or healed pulmonary tuberculosis, one of which was associated with coal miner's pneumoconiosis and another with foci of interstitial and intra-alveolar fibrosis. Two patients had organising pneumonia without evidence of interstitial inflammation or fibrosis; another showed organising fibrinous intra-alveolar exudate in the presence of uræmia. The remaining two patients had bronchiectasis without involvement of bronchioles. Marked interstitial fibrosis was present in one of these and the radiological appearances were similar to those in the cases now discussed in detail. However, the patient had undergone tracheostomy in childhood for diphtheria, so the lung lesions present at autopsy may well be the late result of long-standing chronic bronchitis and bronchiectasis. The absence of rheumatoid granulomata in these fibrosed lungs and in most of the cases of interstitial pneumonia supports the opinion of Rickards and Barrett (1958) that silica, rather than the presence of pre-formed collagen (Gough *et al.*, 1955), is necessary for the formation of the lesions of Caplan's syndrome.

Clinical and radiological information about the patients in the present series is incomplete, but such as is available indicates that the findings are similar to those in the cases already on record. The appearances in the previous cases in which no histological examination was made have also been similar (Leys and Swift, 1949; Bloom and Rubin, 1950; Middleton, 1951; Harris, 1954; Ellman and Cudkowicz, 1954; Aronoff *et al.*, 1955, Case 2; Spence, 1955; Lodge, 1956; Mason and Steinberg, 1957). The main clinical features are thus progressive dyspnœa and cough, often with expectoration and occasionally with chest pain; physical signs are neither marked nor specific. Tracheostomy became necessary in three patients (Hart and Mackenzie, 1955; Ellman, 1956, Case A.L.; Rubin and Lubliner, 1957, Case 51), but was due to local involvement of the larynx in two of these. The radiological appearance of diffuse reticulation has been common to all of the cases and some have also shown mottling or nodulation. These changes have been most pronounced in the mid- or lower zones and were noted by Lodge (1956) in nine out of forty patients with lung involvement. Cystic changes have been mentioned only twice (Aronoff *et al.*, 1955, Case 2; Rubin and Lubliner, 1957, Case 51) and were confirmed histologically in the latter.

The interpretation of the ætiology of the lung changes and their relationship to the basic disease process present some difficulties. Apart from the granulomata in Case 2, none of the lesions encountered in this series can be regarded as specific. Indeed, most of the changes can be seen in cases of chronic bronchitis or peripheral to a bronchial carcinoma and all of them were described by Heppleston (1956) in fifty-three examples of honeycomb lung which were unassociated with any specific ætological factor. The present cases showed no evidence of those specific factors which were present in the remaining thirteen cases of Heppleston's series, nor of other conditions associated with diffuse reticular or nodular radiological changes (Scadding, 1952; Blair, 1955). It

must be admitted that irradiation may have had some influence on the development of the lesions in the case described by Hart and Mackenzie. However, the peripheral distribution of the lung lesions in this case is unlike that of pure irradiation fibrosis (Warren, 1942), and the occurrence of bronchiolectasis seems to be quite unusual after irradiation (Warren and Spencer, 1940; Whitfield *et al.*, 1956). Several authors have described clinical and radiographic evidence of non-specific lung lesions similar to those under discussion in some cases of systemic lupus erythematosus, diffuse acrosclerosis (so-called diffuse scleroderma), polyarteritis nodosa and in the Hamman-Rich syndrome, or have commented on the similarity between the lesions in these conditions (Leinwand *et al.*, 1954; Harvey *et al.*, 1954; Rubin, 1955; Grant *et al.*, 1956; Rubin and Lubliner, 1957; Read, 1958). However, Ellman and Cudkowicz (1954) believe that the clinical and radiological appearances present different patterns in the four chronic rheumatic diseases, and pathological studies indicate that distinctive changes are seen in the lungs in some cases of systemic lupus erythematosus (Baggenstoss, 1952; Purnell *et al.*, 1955) and polyarteritis nodosa (Rose and Spencer, 1957). The characteristic appearance in the Hamman-Rich syndrome of diffuse involvement throughout all lobes (Hamman and Rich, 1944; Rubin and Lubliner, 1957) differs from the more patchy distribution of the lesions in the other diseases, though the actual changes within the lung tissue may be closely similar. Indeed, Rubin and Lubliner consider that some cases of the Hamman-Rich syndrome may be a manifestation of rheumatoid disease.

Full autopsy examination of the patients in the present series did not reveal any evidence of systemic lupus erythematosus, diffuse acrosclerosis, polyarteritis nodosa, or of other conditions likely to have caused the pulmonary fibrosis. On the other hand, all of the patients suffered from classical or definite rheumatoid disease, using the criteria of Ropes *et al.* (1958). Accurate information about the temporal relationship between the development and activity of the lung and joint lesions is not available, but such a connection is not an essential factor in postulating that both are manifestations of rheumatoid disease, for active visceral lesions can be found in a considerable proportion of patients in the absence of active arthritis and vice versa (Cruickshank, 1957). Furthermore it should be remembered that the joint lesions which have for so long been used as the basic criterion for the diagnosis of rheumatoid arthritis are themselves non-specific in the vast majority of patients. It is of interest, and perhaps of significance, that no evidence of pulmonary lesions of the types discussed here has been found in a review of post-mortem protocols and sections from over 200 examples of ankylosing spondylitis (Cruickshank, unpublished). Mallory (1948) found only sixteen examples of interstitial pulmonary fibrosis in a series of 6,000 unselected autopsies. The occurrence of five of the present cases in a series of 100 autopsies suggests a causal rather than a chance relationship between the rheumatoid disease and the pulmonary lesions.

Final assessment of the role of the rheumatoid disease in the ætiology and pathogenesis of interstitial pneumonia and its consequences may have to await further study. In the meantime it is important to recognise the pathological

changes which are responsible for the clinical and radiological features. Although Dixon and Ball (1957) obtained no response to steroid therapy in their case, Ellman (1956) mentions one case in which a striking response occurred. The earliest lesions seen in this series are such that they should be reversible, and steroids may play a part at this stage.

Summary

Clinical, radiological and pathological features are described in eight fresh examples of interstitial pneumonia, pulmonary fibrosis or honeycomb lung associated with rheumatoid disease.

The pathological changes were non-specific, except in one patient who had minute rheumatoid granulomata.

The histological findings are compared with those in previously recorded examples, and it is suggested that the development of interstitial pneumonia and fibrosis leads to bronchiolectasis, which may be of limited or widespread distribution. Honeycomb lung represents the extreme form of the lesion.

The ætiology of the lesions is discussed, with particular reference to irradiation, systemic lupus erythematosus, diffuse acrosclerosis, polyarteritis nodosa and the Hamman-Rich syndrome, and it is concluded that the lung lesions are manifestations of rheumatoid disease.

I am grateful to Prof. J. Gough (Cases 1 and 7) and Dr. H. Spencer (Case 8) for sending me material from their unrecorded cases, and to Drs. J. W. Clegg (Case H.L., Ellman, 1956), J. Ball, F. D. Hart and D. H. Mackenzie for the opportunity to see material from cases already on record.

REFERENCES

Aronoff, A., Bywaters, E. G. L., and Fearnley, G. R. (1955): *Brit. med. J.*, **2**, 229.
Baggenstoss, A. H. (1952): *Proc. Mayo Clin.*, **27**, 412.
Ball, J. (1954): *Ann. rheum. Dis.*, **13**, 277.
Blair, L. G. (1955): *J. Fac. Radiol.*, **6**, 1.
Bloom, J., and Rubin, J. H. (1950): *Canad. med. Ass. J.*, **63**, 355.
Cruickshank, B. (1954): *Ann. rheum. Dis.*, **13**, 136.
(1957): *Proc. roy. Soc. Med.*, **50**, 462.
Cunningham, G. J., and Parkinson, T. (1950): *Thorax*, **5**, 43.
Dixon, A. St. J., and Ball, J. (1957): *Ann. rheum. Dis.*, **16**, 241.
Edge, J. R., and Rickards, A. G. (1957): *Thorax*, **12**, 352.
Ellman, P. (1956): *Postgrad. med. J.*, **32**, 370.
Ellman, P., and Ball, R. E. (1948): *Brit. med. J.*, **2**, 816.
Ellman, P., and Cudkowicz, L. (1954): *Thorax*, **9**, 46.
Gardner, D. L., Duthie, J. J. R., Macleod, J., and Allan, W. S. A. (1957): *Scot. med. J.*, **2**, 183.
Gough, J., Rivers, D., and Seal, R. M. E. (1955): *Thorax*, **10**, 9.
Grant, I. W. B., Hillis, B. R., and Davidson, J. (1956): *Amer. Rev. Tuberc.*, **74**, 485.
Hamman, L., and Rich, A. R. (1944): *Bull. Johns Hopk. Hosp.*, **74**, 177.
Harris, L. H. (1954): *Lancet*, **2**, 119.
Hart, F. D., and Mackenzie, D. H. (1955): *Brit. med. J.*, **2**, 890.
Harvey, A. M., Shulman, L. E., Tumulty, P. A., Conley, C. L., and Schoenrich, E. H. (1954): *Medicine*, **33**, 291.
Heppleston, A. G. (1951): *Thorax*, **6**, 426.
(1956): *Ibid.*, **11**, 57.
Könn, G. (1956): *Beitr. path. Anat.*, **116**, 273.
Leinwand, I., Dunyee, H. W., and Richter, M. N. (1954): *Ann. intern. Med.*, **41**, 1003.

LEYS, D. G., and SWIFT, P. N. (1949): *Brit. med. J.*, **1**, 434.
LODGE, T. (1956): *Brit. J. Radiol.*, **29**, 645.
MALLORY, T. B. (1948): *Radiology*, **51**, 468.
MASON, R. M., and STEINBERG, V. L. (1958): *Ann. phys. Med.*, **4**, 265.
MIDDLETON, J. W. (1951): *Dis. Chest*, **19**, 473.
PRICE, T. M. L., and SKELTON, M. O. (1956): *Thorax*, **11**, 234.
PURNELL, D. C., BAGGENSTOSS, A. H., and OLSEN, A. M. (1955): *Ann. intern. Med.*, **42**, 619.
RAVEN, R. W., WEBER, F. P., and PRICE, L. W. (1948): *Ann. rheum. Dis.*, **7**, 63.
READ, J. (1958): *Amer. Rev. Tuberc.*, **78**, 353.
RICKARDS, A. G., and BARRETT, G. M. (1958): *Thorax*, **13**, 185.
ROPES, M. W., BENNETT, G. A., COBB, S., JACOX, R., and JESSAR, R. A. (1958): *Bull. rheum. Dis.*, **9**, 175.
ROSE, G. A., and SPENCER, H. (1957): *Quart. J. Med.*, **26**, 43.
RUBIN, E. H. (1955): *Amer. J. Med.*, **19**, 569.
RUBIN, E. H., and LUBLINER, R. (1957): *Medicine*, **36**, 397.
SCADDING, J. G. (1952): *Tubercle*, **33**, 352.
SPENCE, M. P. (1955): *Arch. Middx Hosp.*, **5**, 95.
WARREN, S. (1942): *Arch. Path.*, **34**, 917.
WARREN, S., and SPENCER, J. (1940): *Amer. J. Roentgenol.*, **43**, 682.
WHITFIELD, A. G. W., BOND, W. H., and ARNOTT, W. M. (1956): *Quart. J. Med.*, **25**, 67.

Brit. J. Dis. Chest (1959) **53**, 237.

SJØGREN'S SYNDROME

REPORT OF A FATAL CASE WITH PULMONARY AND RENAL LESIONS

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In 1933 Sjøgren gave a full clinical and pathological description of a syndrome of which only single features had previously been reported. The triad by which he characterised the condition consisted of kerato-conjunctivitis sicca, xerostomia, and recurrent swelling of the parotids; but he stressed the generalised nature of the condition in pointing out that these were often accompanied by rheumatoid arthritis and, less frequently, by minor manifestations in other organs (Sjøgren, 1935). Although slowly progressive, Sjøgren's syndrome is hardly ever fatal and only ten autopsies have been reported (table). The present case is reported not only because the patient came to autopsy but because hitherto undescribed lung lesions were found, together with severe renal damage.

The clinical diagnosis of Sjøgren's syndrome is based on the diminution of lacrimal secretion, usually associated with kerato-conjunctivitis, and of salivary secretion, manifested by xerostomia. Biopsy of lacrimal and salivary glands may confirm the diagnosis, but a negative result is not conclusive because the glands may not be uniformly involved (Riva, 1945; Morgan and Raven, 1952; Ehrlich and Greenberg, 1954; Gamp, 1954).

The syndrome chiefly occurs in women over 40 (Sjøgren, 1933, 1951), but although most authors agree on this age and sex distribution, no ætiological relationship with the menopause has yet been proved, all investigations of endocrine function having given normal results. In a clinical study of 121 patients Henderson (1950) concluded that " the menopause has little to do with the onset of the symptoms." Since the onset of symptoms in the present case was in childhood it is of interest that a few cases of Sjøgren's syndrome have been reported in children or adolescents (Lisch, 1937; Coverdale, 1948; Reader, Whyte and Elmes, 1951; Sjøgren, 1953, 1955), some of them with familial incidence, suggesting a congenital defect.

Of the diseases frequently associated with the syndrome, rheumatoid arthritis is the most important, joint lesions being found in about 50 per cent. of cases (Sjøgren, 1933; Holm, 1949). Recent studies of a large number of patients with rheumatoid type of arthritis reveal a high incidence (10-15 per cent.) of kerato-conjunctivitis sicca (Stenstam, 1947; Gaulhofer, 1954; Thompson and Eadie, 1956). Thompson and his colleague even say that " kerato-conjunctivitis sicca is not the rarity it was once considered to be. It is, indeed, the commonest ocular complication of rheumatoid arthritis."

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Sjøgren's syndrome has also been described in association with other forms of collagen disease, such as Felty-syndrome (Friese and Linke, 1950; Gurling, Bruce-Pearson and Pond, 1954), scleroderma (Sheldon, 1938; Leriche, 1947; Holm, 1949; Piazzesi, 1956) and Lupus erythematosus (MacLean and Robinson, 1954; Schaposnik, Bergna and Conti, 1956), which seems to support the idea that the syndrome itself may be a special manifestation of a collagen disease. The failure of the syndrome to respond to cortisone and ACTH treatment (Sjøgren and Eriksen, 1952; Thompson and Eadie, 1956) may be due to destruction of glandular tissue.

Pathological Changes in Lacrimal and Salivary Glands

Knowledge of the pathological changes in this syndrome is based on biopsies of salivary and lacrimal glands and the small number of autopsies (10) hitherto reported. From the work of Sjøgren (1933; 1940), which has since been confirmed (Riva, 1945; Ellman, Weber and Goodier, 1951; Morgan and Raven, 1952; Cardell and Gurling, 1954; Gamp, 1954), certain pathological changes in the salivary and lacrimal glands seem characteristic of the condition, namely loss of the parenchyma, without obvious necrosis, and its gradual replacement by a dense infiltration of lymphocytes and plasma cells (Fig. 1)*, with occasional eosinophils, when the gland may resemble a lobulated collection of lymphoid tissue: a slight increase of interstitial connective tissue: circular islets of big epithelial cells within the " lymphoid " tissue, originally interpreted by Sjøgren as remnants of the glandular parenchyma, but now recognised as secretory ducts of which the epithelium has proliferated (Morgan, 1954).

Morgan (1954) examined parotid and lacrimal glands, although fewer of the latter were available for study. He emphasised that in both the histological changes were similar, save that he did not see proliferation of the duct epithelium in the lacrimal glands, which might explain why these do not enlarge in Sjøgren's syndrome. He also stressed the histological similarity between Sjøgren's syndrome and Mikulicz's disease (a sub-group of Mikulicz's syndrome) and suggested that the two conditions might be identical. As suggested by Riva (1945), however, the term Mikulicz's syndrome should be reserved for cases with symmetrical swelling of the salivary and the lacrimal glands without any major secretory disturbances or serious kerato-conjunctivitis sicca or xerostomia.

A resemblance has been noted between the histological features of Sjøgren's syndrome and polyarteritis nodosa or the rheumatic diseases (Henderson, 1950; Haas, 1951; Beiglböck and Hoff, 1952; Morgan and Raven, 1952; Cardell and Gurling, 1954). In an anatomical study of the case published by Böhm (1950), Haas (1951) found vascular changes in the parotid and lacrimal glands and also in the lymph nodes and the kidneys. Some of the arteries showed mural necrosis and others endarteritis with intimal thickening. He stressed the similarity between his findings and those illustrated by Sjøgren, even suggesting that the illustrations of the latter reveal some vascular change.

* The figure numbers in the text refer to Plates XXXIV-XXXVII.

Pulmonary Features

The lung changes hitherto described in Sjøgren's syndrome are not characteristic (Bruce, 1941; Ellman, Weber and Goodier, 1951; Reader, Whyte and Elmes, 1951; Cardell and Gurling, 1954), including as they do focal and lipoid pneumonia, œdema and hæmorrhage, and a spontaneous pneumothorax shortly before death (Ellman and Weber, 1949). Thompson and Eadie (1956) include pulmonary atelectasis as a complication in 5 of their 18 cases but give no further details. Gordon and Shanbrom (1958) mention " prominence of the vascular markings of a reticular nature." Dry cough, often associated with hoarseness, is frequently mentioned (Weber, 1945; Vannotti, 1948; MacLean and Robinson, 1954; Coverdale, 1955; Thompson and Eadie, 1956; Gordon and Shanbrom, 1958), being usually attributed to diminished mucus secretion. During bronchoscopy Gordon and his colleagues (1958) observed a complete lack of secretion. This has been found by Brouet and Chrétien (1956), who also noted a reduction in the cough-reflex; their microscopic examination of several biopsy specimens revealed numerous goblet cells, apparently staining normally, but also a dense lymphocytic and plasma cell infiltration around the bronchial glands, reduced in number, mainly at the expense of the serous cells. In Ellman, Weber and Goodier's case (1951), (the patient died at the age of 35 from cor pulmonale), Dorothy Russell found a normal number of goblet cells but marked diminution both in size and number of the submucous glands, which displayed all degrees of degeneration and atrophy, with heavy infiltration by lymphocytes and plasma cells and marked dilatation of secretory ducts; the epithelium showed localised squamous-metaplasia. Reader, Whyte and Elmes (1951) mentioned diminished mucous glands; Cardell and Gurling (1954) reported similar changes in one of their cases who died of bronchopneumonia, whereas in the other two the trachea and bronchi were normal.

Renal Features

The table summarises published reports of ten autopsies in cases of Sjøgren's syndrome with particular reference to renal symptoms. The average age at death is 47, though the range was wide. While one patient lived to 73, several died relatively young, five before 38. In most of these cases symptoms were observed in the early twenties, although the usual age of onset is between 30 and 50. Of special interest is the high incidence of renal lesions in these fatal cases, although only three displayed clinical symptoms of uræmia (cases 5, 6 and 9). Two had persistent hypertension (3 and 10), and one a rise in blood pressure shortly before death (case 5). In three patients (1, 6 and 8) the diagnosis made at autopsy was chronic nephritis. In four others (4, 5, 9 and 10) vascular changes were predominant; two (cases 5 and 9) show close similarity, being characterised clinically by a severe hæmorrhagic diathesis and histologically by generalised vascular disease of the type seen in polyarteritis nodosa, and by changes in the kidney. Hæmorrhagic diathesis, usually of Schönlein-Henoch's type, has also been reported in other cases of Sjøgren's syndrome (Bruce, 1941; Leriche, 1947; Holm, 1949; Friese and Linke, 1950).

In contrast to the high incidence of renal lesions functional disturbances of the kidneys in patients with Sjøgren's syndrome are rare. Gordon and Shanbrom (1958) give the only report; isosthenuria, albuminuria, raised serum nitrogen, diminished filtration fraction and hypertension detected during life in a patient with Sjøgren's syndrome.

Case Report

The girl whose case report is given here died, after a long illness, at the age of 22 from a massive cerebral hæmorrhage. It is difficult to unravel and follow many details of her story as they were mostly given by her mother and not by her doctors, since, because of the long and, in many respects, puzzling illness from which she had suffered since childhood, fresh medical advice was repeatedly sought. The disease appears to have started at the age of 9 with a swelling of the parotid glands, diagnosed then as mumps. Thereafter she suffered from severe headaches, recurrent upper abdominal pain with nausea, sore eyes, intermittent parotid swelling and attacks of fever. These affected her recurrently during her whole life.

At the age of 10, 13, 14 and 15 she had severe pneumonia, but the attacks were not unduly protracted and seem to have responded rapidly to antibacterial agents. At the age of 12 she noticed for the first time some difficulty in breathing and was thought to have asthma. Other outstanding symptoms were a slowly progressing curvature of the spine and recurrent joint pains and swelling of the larger joints. The diagnosis of Sjøgren's syndrome was first suggested when she was 13 and, in addition to sore eyes and parotid swelling, complained of a dry mouth. At the age of 14 all her hair fell out and by 16 all her teeth had decayed. Meanwhile she had almost lost her sense of taste and was always troubled by a dry mouth. This was in sharp contrast to a profuse facial perspiration, particularly before the menses, which were otherwise normal. During the last several years of her life she had a recurrent erythematous rash.

All treatment was unsuccessful, including several courses of antibiotic drugs which, although controlling her attacks of pneumonia, evidently did not alter the course of the disease. Corticosteroids were never tried. Her general condition deteriorated slowly until the age of 18, when she started to gain weight and feel stronger. Towards the end of 1956 however, about six months before her death, she again became ill, with cough, pleuritic pain and dyspnœa and with rapid deterioration of her general condition; a diagnosis of " infection and collapse of the lung " was made.

In June 1957 she was admitted to St. Bartholomew's Hospital, London, for the first time. Her general condition was fair and she was able to walk about the ward. Bilateral conjunctivitis was obvious, showing with Bengal Rose the staining characteristic of kerato-conjunctivitis sicca. In Schirmer's test the filter paper was moistened in both eyes for less than 1 mm. (normal more than 15 mm.) after 5 minutes. Parotids and other salivary glands were enlarged and the mouth was very dry. Radiograph of the skull showed that maxillary and frontal sinuses were present with no evidence of sinusitis and that no calculi were visible in the plain radiograph of parotid or submaxillary glands. At sialography the small left duct could not be entered: the right parotid duct was entered with difficulty and in spite of considerable pressure only a small amount

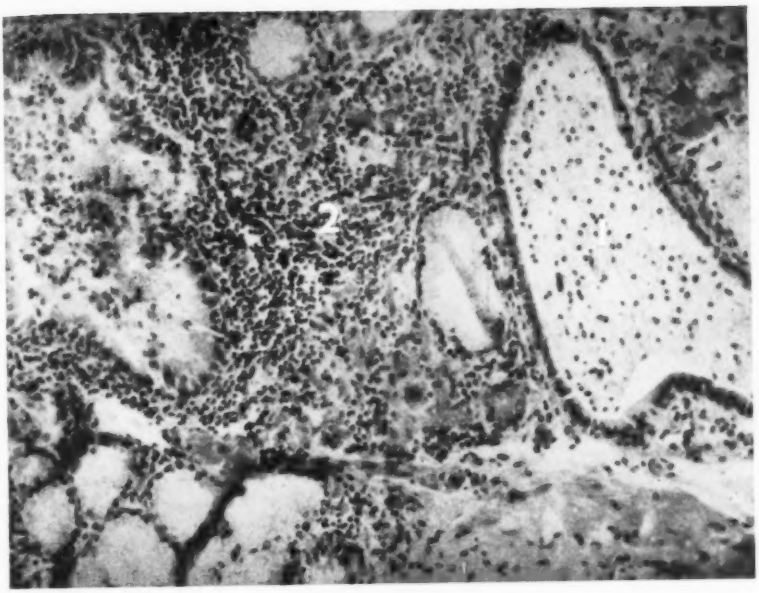

FIG. 1.—Wall of trachea—duct of mucous gland (1), dense lymphocyte and plasma cell infiltration around remnants of acini (2). (H. and E.; M. ×35, E. ×4.)

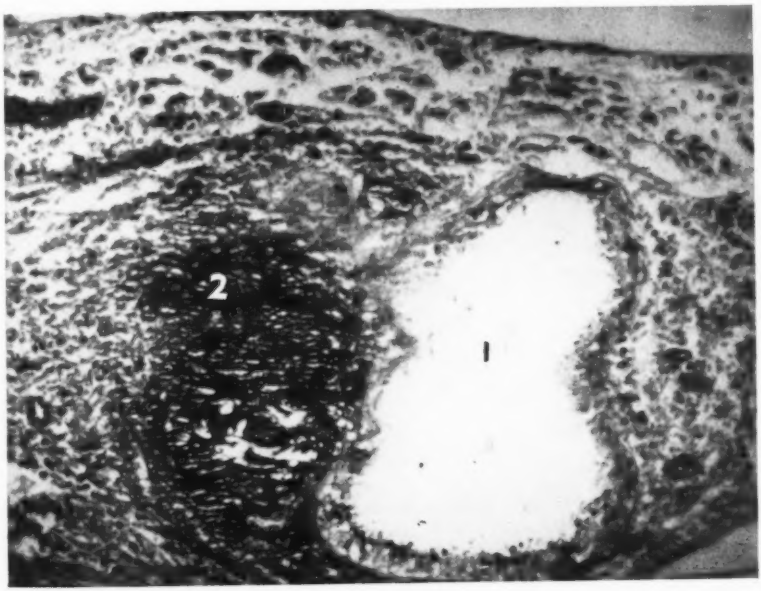

FIG. 2.—Wall of trachea—duct of mucous gland (1) and mucus lying free in wall (2). (Periodic acid Schiff; M. ×35, E. ×4.)

To face p. 240

FIG. 3.—Macroscopic view of cream nodule in lung—granuloma in lung (Fig. 4). (E. ×1.)

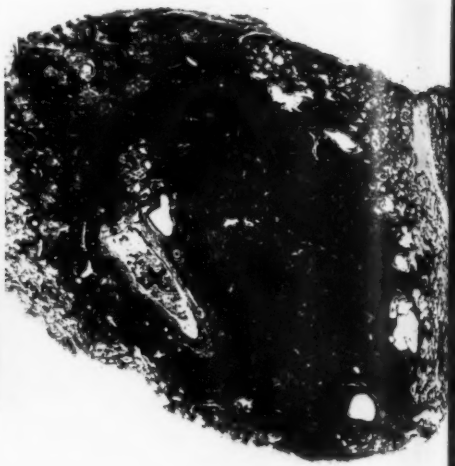

FIG. 4.—Subpleural hyaline nodule (dense black); m solid than Fig. 3; no capsule or adjacent emphys Vessel and bronchioles (X). (H. and E.; M. ×3, E.

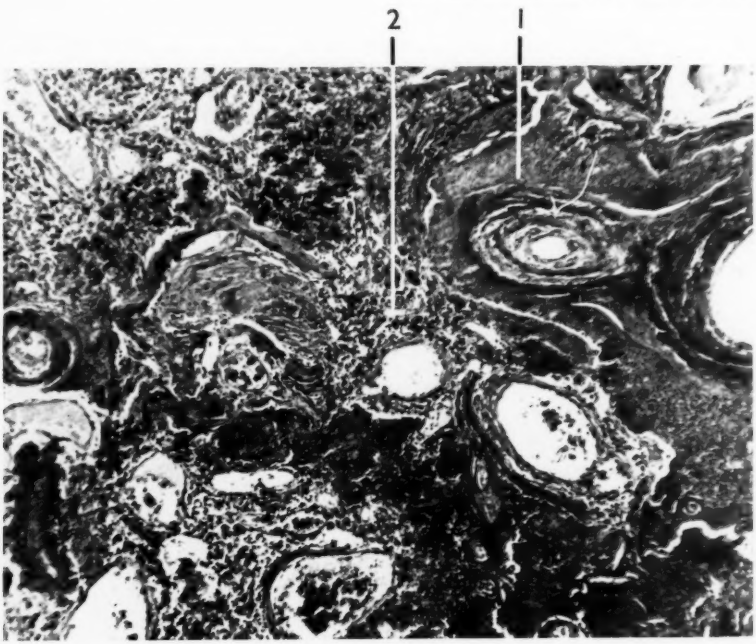

FIG. 5.—Edge of nodule. Hyaline material, mainly in concentric, perivascular arrangement (1). Dense interstitial infiltration of lymphocytes and plasma cells and giant cells (2). (Elastic-van Gieson; M. ×40, E. ×2.)

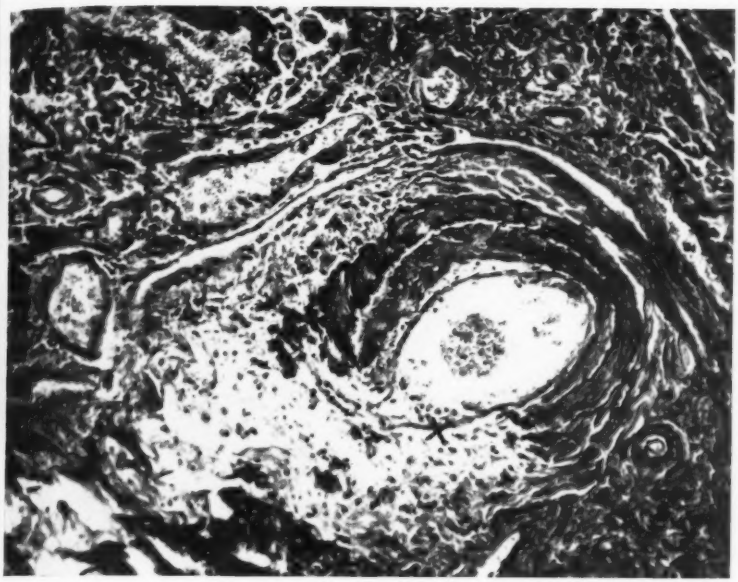

FIG. 6.—From similar lung nodule to that in Fig. 6 showing perivascular infiltration and loss of media of artery (X) without evidence of necrosis. (Elastic-van Gieson; M. ×80, E. ×2.)

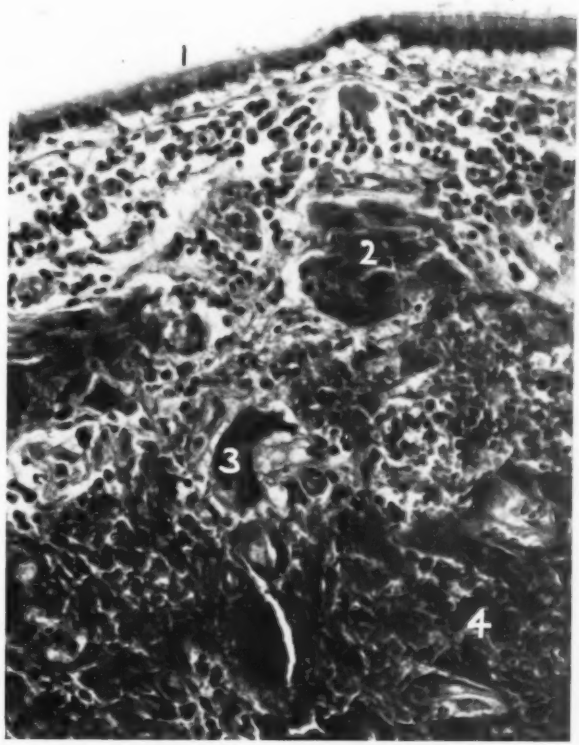

FIG. 7.—From nodule showing intact epithelium of an included bronchiole (1), with cellular infiltration beneath and muscle remnants (2), giant cells (3), and hyaline infiltration (4). (Elastic-van Gieson; M. ×80, E. ×2.)

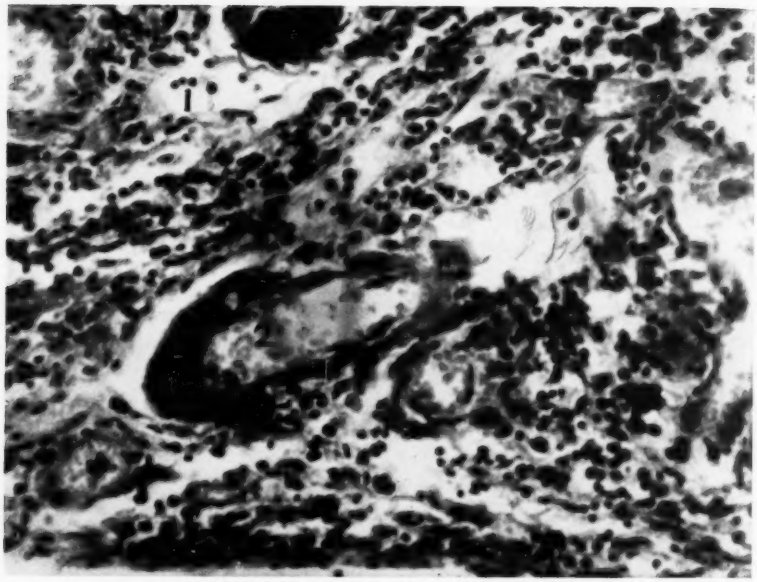

FIG. 8.—From more recent lung lesion (smaller and probably more recent than Figs. 5–7), remnants of alveolar spaces (1) and predominant lymphocyte and plasma cell infiltration. Arteriole with hyaline deposit in wall and perivascular giant cell (2). (H. and E.; M. ×170, E. ×2.)

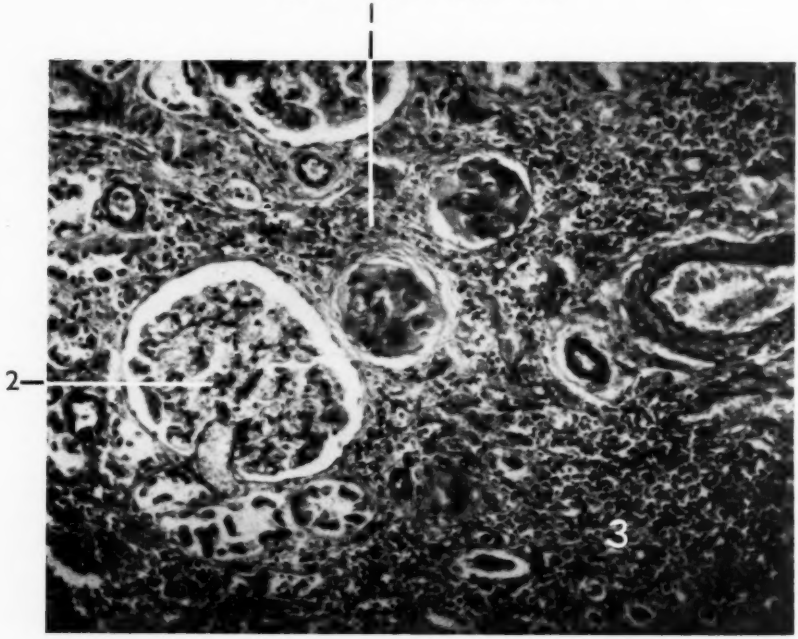

FIG. 9.—Kidney—complete sclerosis and hyalinisation of glomeruli (1), large glomerulus (2) and interstitial infiltration by lymphocytes and plasma cells (3)—the edge of one of the linear zones of infiltration radiating from the pelvis. (Elastic-van Gieson; M. ×35, E. ×4.)

of opaque medium could be injected, which demonstrated the main duct but did not penetrate its finer ramifications.

A chest radiograph showed that the diaphragm was high and that there was gross spinal curvature, but no underlying bone cause was evident. The heart was not enlarged; the right lung was normal.

Further investigations showed that the erythrocyte sedimentation rate was 48 mm. after 1 hour: Hæmoglobin 100 per cent. (14·8 grammes): Leucocyte 8,000/c.mm.

Urinalysis on:	6.6.57	27.6.57
Amount	2,100 ml.	1,650 ml.
Specific gravity	1005	1008
Albumin	+	+

In an attempt to alleviate the ocular symptoms, both lacrimal ducts were closed by electro-coagulation, and pilocarpin was given in an increasing dose ($\frac{1}{20}$ to $\frac{1}{15}$ grains twice a day) and brought considerable improvement in the conjunctivitis. The higher dosage of pilocarpin could not be tolerated because of severe vomiting and was reduced to the smaller. The patient returned home, but within a few weeks, on August 12, 1957, was readmitted urgently with a three days history of severe headache, mainly over the left side, accompanied by continuous vomiting. She had become increasingly somnolent and was semi-comatose. Her blood pressure was 120/80. Two days later some stiffness of the neck and a slight right hemiparesis were noted. The cerebrospinal fluid was at a pressure of 125 mm. of C.S.F. and contained many erythrocytes; 140 mg. per cent. albumin, 260 mg. per cent. chloride and 72 mg. per cent. sugar. A cerebral vascular accident or acute infection was suspected and she died later the same day.

Post-mortem Examination

Post-mortem examination was carried out by Dr. Donald Teare, by whose courtesy the following report is given:

"*External Examination.* Sparely built and rather poorly nourished young adult woman. (Apart from therapeutic puncture marks there was no external injuries.) The parotid glands were easily palpable and hard. There was a little conjunctivitis present in the inner angles of the eyes.

Internal Examination. There was some scoliosis of the dorsal spine to the left.

Central Nervous System. The convolutions of the brain were markedly flattened and medullary coning was present. A large recent hæmorrhage had destroyed most of the left lobe of the brain together with the posterior and inferior parts of the internal capsule and basal nuclei. It was surrounded by some softening but no new growth could be identified.

Circulatory System. The pericardium was adherent to the entire surface of the heart which was dilated throughout. The left ventricle was normal in size; it was slightly brown in colour and rather tough in consistency.

Respiratory System. There were light scattered adhesions in both pleural cavities. Three lesions were found in the lungs. They appeared to be different stages of the same condition. In the lower pole of the right upper lobe the lesion took the form of an oval firm and gritty deposit 1·5 cm. long by 1 cm. wide, which in places appeared to be caseated but showed no surrounding fibrosis.

In the lower lobe of the left lung there was a similar but slightly larger lesion which was not gritty but rather spongy in consistency and this again had no fibrous reaction. In the upper lobe of the left lung there was a vague spongy area somewhat similar to that described above. There was considerable congestion in both lungs. The mediastinal lymph glands were not enlarged.

Stomach. The stomach contained a large quantity of bile-stained fluid; its lining was healthy. Pancreas macroscopically normal. The liver was slightly enlarged and congested throughout, but apparently healthy.

Kidneys were reduced in size by about a third, this reduction being mainly at the expense of the cortex, though the surfaces were extremely granular.

Spleen was enlarged and retained its adolescent lymphoid pattern. The suprarenals were normal.

Parotid glands were firm and surrounded by fibrosis so that their margins were indistinct."

The cause of death was reported as " Cerebral Hæmorrhage due to Chronic Nephritis and Sjøgren's Disease."

Microscopic Examination of Tissue obtained at Autopsy

Method

Tissue was removed during autopsy for microscopic study, fixed in 10 per cent. formalin and embedded in paraffin. In addition to blocks from a routine selection of organs, two from the parotid and one from a submandibular salivary gland were available, and three blocks from different levels of trachea and main bronchi and ten from the lungs, three of these selected from the macroscopically detected lesions, and the remainder at random. Sections 7μ thick from each block were stained with hæmatoxylin-eosin and Verhoeff's elastic van Gieson method. Further investigations of many of the sections were carried out with the following special stains; Unna-Pappenheim Methyl Green-Pyronine, Prussian Blue reaction for iron, Congo Red, Methyl Violet and iodine and sulphuric acid for amyloid, both Weigert's and Mallory's Phosphotungstic acid hæmatoxylin for fibrin, Gomori's stain for reticulin, Periodic-Acid-Schiff reaction (McManus) for mucus. Since all tissue had been embedded in paraffin, stains for fat could not be performed. For more detailed study, particularly of vascular changes, serial sections 7μ thick over a distance of approximately 1 mm. were cut from each of a parotid, a kidney and a lung lesion; sections were cut at several levels from two other lung lesions.

Histological Features

The main changes are in the salivary glands, lungs and bronchi, and kidneys.

Salivary Glands

The lobules of the salivary glands vary in the degree of change. Although no completely normal lobule is present, the lobules of the parotid can still be

recognised, the reticulin pattern being preserved in part, with little increase in the interlobular fibrous tissue: cellular infiltration is present around the large ducts. Often acini are preserved only at the periphery, but in some lobules no acini nor any reticulin pattern remain; only the ducts amidst a diffuse sheet of cells, mainly lymphocytes and small round cells, which include occasional germinal follicles. There is no necrosis. The morphological resemblance of the round cells to plasma cells is so striking that we would identify them as such, their failure to give a positive Unna-Pappenheim-reaction being probably due to formalin fixation (Lillie, 1954). Sjøgren (1940) also referred to the failure of the cells to give stains for plasma cells; his material also was fixed in formalin. Even where the acini are still present and the local cellular infiltration is minimal the reticulin pattern seems disturbed, suggesting that alteration of the reticulin fibres takes place in a very early stage of the disease.

Some of the ducts which remain preserved amidst the cellular infiltrations contain a homogeneous, usually eosinophilic, material which may distend their lumen; in others the lumen is narrowed or even lost, the duct being more or less replaced by a circular compact mass of polygonal rather dark epithelial cells. From various intermediate stages it seems likely that the " islets " of epithelium represent ducts whose lining has proliferated until it has completely filled the lumen (Morgan, 1954).

Dilatation of the vessels occurs within the lobules, but in a score of sections from different levels no evidence of any arteriolar or capillary disease was found and in particular no giant cells or hyaline accumulation as seen in the lung, nor any necrosis of the vessel walls.

The sections from the submandibular gland resemble those of the parotid, although where acini remain they show rather more mucus granules, and multiplication of the duct-epithelium is not evident.

Trachea and Bronchi

The surface epithelium has been preserved at a few sites only, chiefly in the depth of folds and crypts and in comparison with sections of the normal adult bronchus, the number of goblet cells seems not to be diminished. The number and size of mucous glands in the wall also seem within normal limits, but they show similar changes to those in the parotid, namely a patchy atrophy of acini and their replacement by a dense infiltration of lymphocytes and plasma cells (Fig. 1), with a disturbance in the reticulin pattern evident before other changes.

In all parts of the bronchial tree sectioned, including several peripheral bronchi, these changes are seen with no regional difference in severity. Within any gland, changes are patchy and irregular with cells in the mucous phase far more numerous in diseased acini than those in the serous phase.

The ducts, although constricted, as in the normal, close to their opening on to the epithelial surface, are dilated in their deeper parts and sometimes widely distended with secretion containing pyknotic nuclear remnants. Where acinar loss has been more complete mucus may be seen lying free in the tracheal wall (Fig. 2) surrounded perhaps by inflammatory cells but without evidence of

previous acinar structure—a change peculiar to the tracheal wall. Neither the adventitia of the bronchi nor of the blood vessels shows any evidence of disease.

Lungs

Large Cream Nodules. All blocks of tissue include the pleura and, in all, the lesions lie close to the pleura which is thickened from an increase in fibrous tissue mostly internal to its elastic layer. Three nodular lesions (each between 1·5 and 2·0 cm. in diameter) were obvious to the naked eye (Fig. 3) and are described separately, although they are probably similar in nature to the smaller more acute lesions detected microscopically. They are somewhat irregular in shape, but well-defined although with no definite capsule; to the naked eye they appear cream, two being solid while the other was spongy. Their relatively small size and subpleural position probably explain their failure to show in a radiograph.

Microscopically a nodule is sharply limited from surrounding lung but without a definite capsule (Fig. 4), while within it the lung pattern can only be detected with difficulty, as even with elastic stain only occasional elastic remnants are demonstrated. The nodules consist mainly of sheets and strands of an amorphous, highly eosinophilic material often arranged concentrically around small arteries, arterioles and even capillaries, between or even internal to the elastic layers of the vessel walls (Fig. 5).

Some of the vessels do show cellular infiltration within their wall, others show loss of the whole medial layer or sometimes of an internal or external elastic membrane suggesting earlier damage. These changes usually affect only part of the circumference (Fig. 6) and may be found in the larger arteries included in the nodules as well as in the arterioles. Unlike the eosinophilic infiltration described above these lesions resemble the scars left in polyarteritis nodosa, although the typical earlier changes of fibrinoid necrosis and polymorpho-nuclear infiltration were not found.

In spite of numerous special strains the precise chemical nature of these deposits could not be established. In particular they are not amyloid (from congo-red, methyl violet and iodine-sulphuric acid stains) although their distribution is similar, or fibrin (from Weigert's stain and Mallory's phosphotungstic acid hæmatoxylin method (PTAH), or collagen (from van Gieson's stain). Their main staining properties are high eosinophilia and argyrophilia, a faint pink staining with Periodic-Acid-Schiff (McManus) and orange-red with Mallory's PTAH. From this histochemical behaviour they can best be described as hyaline. Cameron (1952), discussing such infiltrations, emphasised the close relation between amyloid and its variants and hyaline and described the latter as " among the mysteries of chemical pathology." The giant cell response is not characteristic of amyloid.

In clefts in this eosinophilic material lie numerous lymphocytes and plasma cells. In the middle of one of the nodules lies a bronchiole (Fig. 7), whose epithelium is still intact although the wall is involved right to its base. The bronchial arterioles themselves seem to be spared although their capillaries are involved. At the edge of the lesions there is slight cellular infiltration and

adjacent alveoli are somewhat larger and thinner walled, but otherwise the surrounding lung seems normal. The absence of distortion of the surrounding lung suggests that the nodule represents an infiltration or consolidation and not scarring or loss of tissue. No necrotic areas could be detected even in sections at different levels throughout the nodules.

Acute Changes. In the other blocks of tissue a range of changes is seen which probably represents earlier and more acute phases of the process responsible for the nodules. The areas of disease are well demarcated from surrounding lung and again the lesions form nodules sharply defined although smaller than the cream ones described above. They vary in size up to 1 cm. in diameter, with a strip of subpleural consolidation in one, 2·5 cm. on its pleural surface and extending into the lung to a depth of 0·6 cm. The alveolar pattern can still be recognised within these foci in which consolidation has often arisen from diffuse infiltration, both in the alveolar wall and within the alveolar spaces, by lymphocytes and plasma cells, sometimes associated with a considerable number of giant cells. The main changes are in the walls of the small arteries, arterioles and even capillaries (Fig. 8). Eosinophilic material of the nature described above is present in concentric layers around the small vessels lying within the alveolar wall. Many multi-nuclear cells and a dense cellular infiltration surround these deposits. Patchy endarteritis is present in some vessels and in others has progressed to obliteration. In one section the consolidation is not evenly distributed, some alveoli and small bronchioli being spared, which gives an irregular and rather spongy appearance. In some of the acute lesions cellular infiltration and multinuclear cells are mainly confined to the alveolar wall with œdema the only intra-alveolar change. Infrequently epithelium of the bronchioles is lost and their walls are replaced in part by granulation tissue.

Even in the acute lesions the cellular infiltration consists mostly of plasma cells and lymphocytes, polymorphs being conspicuously absent. The features of giant cell formation, lymphocytes and plasma cells suggest a sub-acute or chronic change, and the failure of the exudate to stain for fibrin also suggests the process is sub-acute.

These changes were seen in nine of the ten blocks of tissue, in the remaining one congestion of alveolar capillaries was the only change, suggesting that the pneumonitis is always associated with arteritis. As pleura was included in all ten sections available it can only be surmised that the deeper part of the lung was similarly affected.

These nodules are unlikely to be infarcts as they lack the characteristic pattern of elastic fibres, and iron is absent; furthermore the more acute lesions do not show hæmorrhage.

Although the exact nature of the joint pains in this patient is not known, the possibility of their being rheumatoid cannot be excluded; but the nodules do not resemble those previously described in rheumatoid arthritis (Christie, 1954), which are characterised by central necrosis and palisading of fibrous tissue in the capsule of the lesion.

The arrangement of the giant cells in close association with the changes of the blood vessels, as well as the absence of necrosis, excludes Wegener's granu-

lomatosis, or an aspiration or lipoid pneumonia, as the reason for the giant cells. No infective agent, either bacterial or fungus, could be found.

The change is essentially a sub-acute, non-infective, exudative pneumonitis, associated with a giant cell vasculitis. Consolidation of lung is from exudate and chronic inflammatory cells which are relatively sparse in number; the vasculitis affects small arteries, arterioles and capillaries. Although these vascular changes in the lung may be quite distinct from Sjøgren's syndrome, arterial damage has previously been described in other organs, which at least makes it probable that in this patient they are part of the pattern of the disease.

Kidneys

In sections from both kidneys occasional glomeruli appear normal, but most are diseased, and demonstrate a wide range of changes (Fig. 9). Many are smaller than normal, some are hypertrophied. Subcapsular exudate is present, which in some instances has organised, producing adhesions between the glomerular tufts or forming crescents, and in others the degree of hyaline fibrosis is such that the glomeruli are replaced by hyaline nodules. The tubules also show wide variation both in size and degree of damage, some being so distended with clear eosinophilic material that they appear as a retention cyst. The tubular epithelium is necrotic in some instances, probably the result of post-mortem change. Capillary dilatation is widespread but little disease of the afferent arterioles is seen beyond slight arteriolo-sclerosis: larger arteries show nothing beyond slight end-arteritis. In the peripelvic tissue which, unfortunately, is included at only one corner of the section no inflammatory response is present. The hyalinisation of glomeruli seems out of proportion to the vascular changes which could be secondary to the glomerular lesions. Dense interstitial infiltrations of lymphocytes and plasma cells are striking and have a linear distribution radiating from the pelvis. Interstitial connective tissue is not increased. No necrosis of vessel wall nor peri-vascular deposits similar to those in the lungs were seen. Dense infiltrations with lymphocytes and plasma cells lie between the tubules of the medulla. The appearances do not correspond to those found in lupus erythematosus or polyarteritis nodosa, and since a " necrotic and proliferative vasculitis " is not present, these changes do not resemble those described by Haas (1951) in a case of Sjøgren's syndrome. The renal lesions are those of a glomerulitis and an interstitial nephritis. The resemblance of the cellular exudate to that found in the salivary glands and elsewhere in this patient suggests that this may be also a manifestation of the disease.

Heart: Muscle fibres are of approximately equal size, with no fibrosis and no changes of the blood vessels. Pericardium is not included in the section.

Œsophagus is lined by stratified squamous epithelium. In the submucosa the œsophageal glands show similar changes to those described in the parotids and bronchial glands; in some only the ducts can be recognised, the acini being completely replaced by lymphocytes and plasma cells. Granules staining by Periodic-Acid-Schiff method are present at the luminal edges of the gland cells and several of the ducts are full of similar material.

Small intestine and colon. No evidence of abnormality.

Liver. The liver cells are within normal limits save for an occasional single large vacuole in the cytoplasm. Although the large portal canals are normal the smaller ones show heavy cellular infiltrations without evidence of new duct formation. Fibrous tissue is not increased, either in the capsule or parenchyma, and there is no evidence of amyloid infiltration.

Pancreas. Much of the pancreas is normal save for post-mortem autolysis, but at several sites the acinar tissue is replaced by vascular connective tissue with heavy cellular infiltration and loss of reticulin pattern.

Spleen. The malpighian bodies are small and the red pulp is much increased, the endothelial cells being numerous and the intersinusoidal framework thickened.

Lymph node shows only a few germinal centres with an increase in the reticulo-endothelial elements.

Suprarenal within normal limits.

In summary then, at autopsy in the parotid and submaxillary glands the changes previously described in cases of Sjøgren's syndrome were found, atrophy of parenchyma, with infiltration by lymphocytes and plasma cells, persistence of ducts with little fibrosis: in addition, similar changes were found in the mucous glands of the trachea and bronchi and œsophagus, and the early disturbance of the reticulin pattern was noted. The kidneys showed interstitial cellular infiltration, similar in nature to that found in other organs, together with hyalinising glomerular lesions of widely varying age. The lungs exhibited a peculiar giant-cell vasculitis, involving arteries, arterioles and even capillaries. It was associated with nodules of hyaline material, up to 2 cm. in diameter, and with more acute lesions of an exudative pneumonitis in which the same hyaline material was present in smaller amounts. Inflammatory cells, lymphocytes and plasma cells were relatively sparse. These vessel changes were not found in any other organ examined.

Discussion

Diagnosis and Clinical Course

The diagnosis of Sjøgren's syndrome in this case was made during life on the grounds of the usual clinical symptoms and signs, confirmed at post-mortem by the histological findings in the salivary glands. In addition, we would draw attention to early disturbance of the reticulin pattern.

After a slowly progressive illness the patient died at the age of 22 from an acute cerebral hæmorrhage. This unusual incident in a young woman raises the question of its possible connection with Sjøgren's syndrome. Autopsy did not show an aneurysm, tumour or evidence of general hæmorrhagic diathesis. Hypertensive encephalopathy might have been associated with the bilateral renal lesions, but no evidence of hypertension was found, either during life or at necropsy; the blood pressure shortly before death was 120/80 and no changes in the ocular fundi were seen nor was the left ventricle hypertrophied. The minute structure of the cerebral vessels is not known, since no brain tissue was available for microscopic examination. The only case in the literature of a

patient with Sjøgren's syndrome dying from a cerebral cause is that of a woman of 35 (Holm, 1949) who had a hæmorrhage from an aneurysm of the anterior communicating artery.

Some symptoms displayed by the patient seem not to be associated with Sjøgren's syndrome, outstanding among them being the curvature of the spine which, appearing first at the age of 10, progressed to severe kypho-scoliosis. The nature of this " juvenile scoliosis " remains obscure. Other symptoms displayed by the patient, as *e.g.* alopecia, headache, excessive facial perspiration and recurrent skin rashes, have been reported with other features of the Sjøgren's syndrome, and early decay of teeth seems to be one of the most frequent associations, having been reported in about 90 per cent. of cases.

The frequent attacks of nausea, vomiting and gastric pain suggest changes in the gastric mucosa similar to those in the salivary glands, as reported in cases of Sjøgren's syndrome by Lisch (1937), Weber (1945), Beiglböck and Höff (1952) and Morgan and Raven (1952). Although Sjøgren (1940) himself denied a connection of the gastric lesions with the " sicca syndrome," and Gordon and Shanbrom (1958) describe a normal histological picture of the gastric mucosa in their case. No information is available on the quality and quantity of gastric secretion in our patient, nor on the appearance of the gastric mucosa. In the œsophagus, lesions similar to those in the salivary glands were found, the submucosal glands being partly replaced by dense infiltrations of round cells, but small intestine and colon which were studied histologically show no characteristic lesion.

Pulmonary Changes

The lesions in the respiratory system are of interest as, together with those in the kidney, they emphasise widespread involvement by this disease. Episodes of respiratory disease recur in this patient's clinical history, being described as " acute attacks " of high fever with cough, little or no sputum and sometimes pain of a pleural nature not unduly protracted and seeming to respond to antibacterial therapy. Between these attacks the patient apparently did not suffer from cough; once only dyspnœa of the " asthmatic " type was recorded.

In the trachea and bronchi histological examination revealed changes comparable to the ones in the parotids. In contrast to the findings in the lungs previously described (Ellman, Weber and Goodier, 1951; Reader, Whyte and Elmes, 1951) reduction in the number of submucous glands was not obvious, but with resolutions of the inflammatory exudate and if the atrophy had progressed, the final appearance would have been of a striking reduction in the glands. The pulmonary lesions found in our patient are different from those previously described in cases of Sjøgren's syndrome, nor did they closely resemble any other known disease.

The pulmonary lesions share one feature with the salivary glands and kidneys—a patchy accumulation of lymphocytes and plasma cells. In the lung the additional features are nodules of amorphous hyaline deposits and an arteritis of small blood vessels. Further study of serum proteins in cases of Sjøgren's syndrome may help to determine the relative importance for such

TABLE I

No.	*Author*	*Year*	*Sex*	*Age*	*Symptoms*	*Mode of death*	*Underlying condition*	*Blood pressure*	*Histological changes in kidneys*
1	Sjøgren	1933	F	66	K2, R2	Acute cardiac failure	Chronic nephritis	Not reported	Not reported.
2	Bruce	1941	F	32	P7, X, K, skin macular exanthem, R	Acute ileus		Not reported	Glomeruli; thickened basement membranes, protein precipitate.
3	Holm	1949	F	35	R8, K6, X6, decayed teeth	Subarachnoid hæmorrhage from aneurysm	Essential hypertension	200/130	Nephrosclerosis.
4	Ellman (Russell)	1951	F	35	Raynaud 22, P14, X9, K5, Pleuritis sicca 3, R1	Right heart failure	Spontaneous pneumothorax	100/70	Slight thickening of capillary basement membrane.
5	Haas (Böhm)	1951 (1950)	F	60	X9, R4, P3, K3	Pulmonary œdema, hæmorrhagic diathesis (melæna, hæmoptysis)	Malignant hypertension	120/80—230/130	Acute necrotising arteriolitis.
6	Reader	1951	F	30	X11, P11, R2, K?, teeth decayed	Aspiration pneumonia. Terminal pleuritis and pericarditis. (?Uræmia)	Chronic pyelonephritis	120/65	Chronic pyelonephritis (with fibrosis of glomeruli and tubules).
7	Morgan Raven	1952	F	58	R15, X4, P2, K2	Cerebral embolism	Recent thrombosis in right arm	Not reported	
8	Cardell	1954	F	38	R16, P10, X4, K4	Bronchopneumonia	Acute pancreatitis	130/70	Scarring—chronic pyelonephritis.
9	Cardell	1954	F	49	R20, P8, K4, X4	Uræmia	Periarteritis nodosa, hæmorrhagic diathesis	120/70	Periarteritis nodosa.
10	Cardell	1954	M	73	P10, X5, K4, swelling of lacrimal glands	Cerebral thrombosis, bronchopneumonia	Atheroma	230/110	Arteriosclerosis.

K = Kerato-conjunctivitis sicca. X = Xerostomia. R = Rheumatoid arthritis. P = "Parotitis."
(Figures represent duration in years.)

exudation of changes in vessel wall or in circulating serum. Although the arteritis was confined to the lungs in this case, vascular involvement has been observed in salivary glands, lymph nodes and kidneys of other cases with Sjøgren's syndrome (Haas, 1951; Morgan and Raven, 1952; Cardell and Gurling, 1954) and it is possible that these changes are similar.

Renal Changes

In spite of the well-developed renal changes, the only signs possibly related to renal disease were chronic headache, nausea and slight albuminuria with low specific gravity of urine. Such paucity of clinical manifestations is not uncommon in chronic renal disease (Raaschou, 1948), which may account for the lack of clinical evidence of renal involvement in Sjøgren's syndrome. In their recent report of renal disorder in life Gordon and Shanbrom (1958) have suggested that such renal lesions are part of Sjøgren syndrome. The frequent autopsy finding of renal lesions of one sort or another (table) suggests that in some way these are related to Sjøgren's syndrome, although it is unlikely that this is consequent on primary disease of the kidneys, since changes in mucous membranes usually only appear when other symptoms of uræmia are present. Furthermore kerato-conjunctivitis sicca has not been described as a symptom of chronic nephritis. Although various types of renal lesion are reported in patients with Sjøgren's syndrome in several cases, including our own, these include infiltration with lymphocytes and plasma cells such as occurs in other organs. Vascular changes have also been reported in salivary and lacrimal glands and kidneys (Haas, 1951; Ellman, Weber and Goodier, 1951; Cardell and Gurling, 1954). In this case neither the kidneys nor the parotids showed primary vascular changes, but only the lung nodules.

In future it will be interesting to look for clinical manifestations of kidney disease in all cases of Sjøgren's syndrome.

Significance of the Pathological Changes

Our own findings and the reports in the literature suggest that Sjøgren's syndrome, besides being clinically a well-defined entity, has a recognisable pathological picture characterised by atrophy of the parenchyma of salivary and lacrimal glands and also of those in the bronchial wall and œsophagus and its replacement by dense infiltrations of lymphocytes and plasma cells. An early change in the glands is the irregularity or loss of the reticulin pattern; fibrosis is not a striking feature. These changes have been associated with vascular lesions sufficiently frequently to suggest that these play an important if yet undefined part. The vascular changes may occur in only one organ and can be a necrotising type of arteritis or a perivascular giant cell arteritis with hyaline deposits as in this case.

The "lymphoid" appearance of the salivary glands resembles the histological pattern in lymphadenoid goitre (Hashimoto's disease) (Ellman and Weber, 1949; Gruber, 1956; Gordon and Shanbrom, 1958). Recently in the latter disease specific antibodies have been demonstrated and the suggestion made that it results from an 'auto-immune process' (Roitt and Doniach, 1958).

Jones (1958) has recently demonstrated similar precipitating antibodies to tissue of lacrimal and salivary glands from six patients with Sjøgren's syndrome and suggested a similar mechanism. However, it cannot yet be said whether in Hashimoto's disease these manifestations are the cause of the disease (*Lancet* editorial, 1958) or only a measure of the nature and degree of damage to the thyroid.

The histological features of Sjøgren's disease suggest that in general terms nutritional disturbance in the cells occurs early, as witnessed by the alteration in reticulin pattern, without necessarily any infiltration by inflammatory cells; the parenchymal cells atrophy, their disappearance being so slow that necrotic cells are not usually seen. But it may be that such death of cells results in the release into the blood of cell contents usually properly contained within its membrane or at least escaping only in small amounts. Such release of intracellular substances might explain both the presence of auto-antibodies in serum as well as the infiltrations by plasma cells and lymphocytes, cells concerned with antibody production.

The varied manifestations of the disease in our patient leave undecided whether Sjøgren's syndrome is of a generalised nature, protean in its manifestations but the result of a particular and single cause, or whether, in fact, there are a variety of causes which can give rise to the various changes which have become identified with the name.

Summary

This paper reports a fatal case of Sjøgren's syndrome. The patient, a girl, died at the age of 22 from massive cerebral hæmorrhage. The syndrome was diagnosed at 13 when the triad kerato-conjunctivitis sicca, xerostomia and parotid swelling had all developed, together with joint pains and scoliosis.

At autopsy the lacrimal and salivary glands showed the characteristic atrophy of parenchyma with lymphatic infiltration, a similar picture being seen in the mucous glands of the bronchi and œsophagus. In the lungs a type of lesion not previously described was found—nodules of hyaline material several centimetres in diameter and associated with arteritis, as well as smaller, probably earlier, changes of exudative pneumonitis with giant cell arteritis. Arterial changes were confined to the lungs and involved the smallest arterioles as well as larger vessels. The kidneys showed varying stages of glomerulitis and interstitial infiltration with plasma cells and lymphocytes.

We are grateful to Dr. N. C. Oswald for referring this case to us for detailed study and to Dr. D. Teare for the report of the autopsy he carried out; to Dr. A. G. Stansfeld for sending us the paraffin blocks and sections; and to Mr. D. F. Kemp of the Photographic Department of the Institute of Diseases of the Chest for the photographs.

REFERENCES

BEIGLBÖCK, W., and HOFF, H. (1952): *Dtsch. med. Wschr.*, **77**, 7 and 42.
BOHM, A. (1950): *Münch. med. Wschr.*, **92**, 955.
BROUET, G., and CHRÉTIEN, J. (1956): *Les Bronches*, **6**, 7.
BRUCE, G. M. (1941): *Arch. Ophthal., N.Y.*, **26**, 945.

CAMERON, G. R. (1952): " Pathology of the Cell," p. 337. Edinburgh: Oliver and Boyd.
CARDELL, B. S., and GURLING, K. J. (1954): *J. Path. Bact.*, **68,** 137.
CHRISTIE, G. S. (1954): *Aust. Ann. Med.*, **3,** 49.
COVERDALE, H. (1948): *Brit. J. Ophthal.*, **32,** 663.
(1955): *N.Z. med. J.*, **54,** 641.
EHRLICH, J. C., and GREENBERG, D. (1954): *Arch. intern. Med.*, **93,** 731.
ELLMAN, P., and WEBER, F. P. (1949): *Brit. med. J.*, **1,** 304.
ELLMAN, P., WEBER, F. P., and GOODIER, T. E. W. (1951): *Quart. J. Med., N.S.*, **20,** 33.
FRIESE, G., and LINKE, A. (1950): *Dtsch. med. Wschr.*, **75,** 980.
GAMP, A. (1954): *Medizinische*, No. 40, 1347.
GAULHOFER, W. K. (1954): *Acta med. scand.*, **149,** 441.
GORDON, M. E., and SHANBROM, E. (1958): *Ann. intern. Med.*, **48,** 3142.
GRUBER, E. (1956): *Arch. Ophthal., N.Y.*, **55,** 42.
GURLING, K. J., BRUCE-PEARSON, R. S., and POND, M. H. (1954): *Brit. J. Ophthal.*, **38,** 619.
HAAS, E. (1951): *Virchows Arch. path. Anat.*, **320,** 264.
HENDERSON, J. W. (1950): *Amer. J. Ophthal.*, **33,** 197.
HOLM, S. (1949): *Acta ophthal., Kbh., Supp.*, **33.**
JONES, B. R. (1958): *Lancet*, **2,** 773.
Lancet editorial (1958): 1049.
LERICHE, R. (1947): *Pr. méd.*, **55,** 77.
LILLIE, R. D. (1954): " Histopathologic Technique and Practical Histochemistry." New York: Blakiston.
LISCH, K. (1937): *Arch. Augenheilk.*, **110,** 357.
MACLEAN, K., and ROBINSON, H. S. (1954): *Canad. med. Ass. J.*, **71,** 597.
MORGAN, W. S. (1954): *New Engl. J. Med.*, **251,** 5.
MORGAN, A. D. and RAVEN, R. W. (1952): *Brit. J. Surg.*, **40,** 154.
PAYNE, R. T. (1933): *Lancet*, **1,** 348.
PIAZZESI, W. (1956): *Riv. Patol. nerv. ment.*, **77,** 584.
RAASCHOU, F. (1948): " Chronic Pyelonephritis," Copenhagen: Munksgaard.
READER, S. R., WHYTE, H. M., and ELMES, P. C. (1951): *Ann. rheum. Dis.*, **10,** 288.
RIVA, G. (1945): *Schweiz. med. Wschr.*, **75,** 376.
ROITT, I. M., and DONIACH, D. (1958): *Lancet*, **2,** 1027.
RUBIN, P., and HOLT, J. F. (1957): *Amer. J. Roentgenol.*, **77,** 575.
SCHAPOSNIK, F., BERGNA, L. J., and CONTI, A. (1956): *Pren. méd. argent.*, **43,** 897.
SHELDON, J. H. (1938): *Proc. roy. Soc. Med.*, **32,** 255.
SJØGREN, H. (1933): *Acta ophthal. (Kbh.), Supp.*, **2,** 1.
(1935): *Acta ophthal. (Kbh.)*, **13,** 1.
(1940): *Acta ophthal. (Kbh.)*, **18,** 363.
(1951): *Acta ophthal. (Kbh.)*, **29,** 33.
(1953): *Klin. Mbl. Augheilk.*, **122,** 554.
(1955): *Acta ophthal. (Kbh.)*, **33,** 557.
SJØGREN, H., and ERIKSEN, A. (1952): *Acta ophthal. (Kbh.)*, **30,** 463.
STENSTAM, T. (1947): *Acta med. scand.*, **127,** 130.
THOMPSON, M., and EADIE, S. (1956): *Ann. rheum. Dis.*, **15,** 21.
WEBER, F. P. (1945): *Brit. J. Ophthal.*, **29,** 299.
VANNOTTI, A. (1948): *Helv. med. Acta*, **15,** 511.

Brit. J. Dis. Chest (1959) **53**, 253.

HYPOPLASIA OF THE PULMONARY ARTERIES

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The term " unilateral emphysema " has been used to describe a group of cases which presents with increased radiolucency of part or the whole of one lung. Although emphysema is usually a generalised disease, it may be confined to one segment of the lung. When this is the case, that segment occupies more space than normal and this can readily be recognised on a radiograph. Emphysema is, however, but one of a variety of pathological processes which may produce increased radiolucency. This appearance is due to a decrease in the size and number of the pulmonary blood vessels in the area. It may be seen in bronchiectasis, or in bronchogenic carcinoma, due to spreading out of the vessels secondary to compensatory expansion in a lobe adjacent to the collapsed segment. Less frequently, areas of increased radiolucency may occur in a bronchiectatic lobe itself. When partial bronchial obstruction is present overdistension of the lobe distal to the block gives rise to increased radiolucency accompanied by displacement of adjacent structures. Diminished vascularity may also be caused by thrombosis of a pulmonary artery (Shapiro and Rigler, 1948) or by neoplastic occlusion of the artery.

There is another group of cases, forming the subject of this paper, in which the pulmonary artery in the affected segment is hypoplastic. The characteristic radiological features are:

1. The whole of one pulmonary artery, or of one of its lobar branches, is diminished in size. The segmental arteries are also reduced in size and in number.
2. Increased radiolucency of one lung or of one or two of its lobes is evident, owing to this decrease in vascularity.
3. The affected area of lung is decreased in size.

Since the publication of 3 cases of hypoplasia of a lobar pulmonary artery in 1957 we have collected a further 9 examples, and also 4 additional cases in which the whole of the pulmonary artery on one side was affected.

Clinical Presentation

The details of the presentation of these 13 new cases is given in Table I. Only one was a woman and this dominant male incidence was also seen in other published series (Table II). The average age of the patients was 45 years, with extremes of 18 and 58. The condition was discovered either at routine X-ray or following the development of the variety of symptoms for which

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TABLE I.—SUMMARY OF THE HISTORY AND FINDINGS IN THE 13 PATIENTS

Case No.	*Age yrs.*	*Sex*	*Site*	*Angio*	*Bronchogram*	*Effort disability*	*Childhood illness*	*History*
1	58	M.	R.L.Z.	+	Peripheral "blobs"	Mild	0	5 weeks cough.
2	49	M.	L.L.Z.	+	Normal	0	0	Chest pain.
3	42	M.	R.L.Z.	+	No dilatation Slight crowding	0	at 2 yrs.	Productive cough.
4	39	M.	R.L.Z.	+	A few "blobs" peripherally	Moderate	0	20 years increasing bronchitis.
5	54	M.	R.L.Z.	+	Mod. tubular dilatation	Severe	0	20 years increasing bronchitis.
6	28	M.	L.L.Z.	+	Mild tubular dilatation	0	at 1 yr.	Cough and haemoptysis.
7	46	M.	R.L.Z.	+	Normal	0	0	Cough and hæmoptysis.
8	45	M.	R.L.Z.	+	No dilatation Slight crowding	0	0	10 years cough.
9	49	M.	R.L.Z.	+	One large "blob" Spidery bronchi	Mild	0	Cough and dyspnœa.
10	49	M.	L. lung	+	Spidery bronchi	Moderate	at 8 yrs.	Progressive dyspnœa.
11	55	M.	L. lung	+	Moderate tubular dilatation in L. lower lobe only	Moderate	at 8 yrs.	Increasing bronchitis.
12	41	F.	R. lung	0	0	0	0	No symptoms.
13	32	M.	L. lung	0	0	0	0	No symptoms.

TABLE II.—SUMMARY OF CASES PREVIOUSLY REPORTED

Author	*Age*	*Sex*	*Site*	*Comments*
Swyer and James ..	6	M.	R. lung	Three attacks of pneumonia.
Dornhorst *et al.* ..	17	M.	L. lung	Dyspnœa. Pneumonia æt. 7 and 11.
	35	M.	R. lung	Dyspnœa.
	?	M.	R.U.L.	Cough and sputum.
	?	F.	L. lung	Mass X-ray.
Macleod	41	F.	L. lung	Progressive dyspnœa and bronchitis.
	25	F.	L. lung	Cough.
	32	M.	R. lung	Cough and hæmoptysis.
	34	M.	R. lung	Dyspnœa.
	40	M.	L. lung	Cough and dyspnœa.
	32	M.	L. lung	Cough, dyspnœa and wheeze.
	35	M.	R. lung	Dyspnœa and bronchitis.
	18	M.	L. lung	Mass X-ray.
	18	M.	L. lung	Mass X-ray.

patients are referred to a chest clinic (Table III). There was no characteristic history, but on direct questioning 4 patients recalled a " severe chest infection " during childhood or adolescence.

TABLE III.—SUMMARY OF THE CLINICAL PRESENTATION IN THE 13 PATIENTS

	One lobe affected	*One lung affected*
History of chest infection in childhood	2	2
Dyspnœa	4	2
" Bronchitis "	10	1
Hæmoptysis	2	0
No symptoms	0	2

SITE

Of the 9 cases in which a lobar artery was affected, 7 were on the right side and the lower lobe trunk was involved in all. In the 4 in which the whole pulmonary artery on one side was affected, one was on the right and 3 were on the left.

RADIOLOGICAL APPEARANCES

Increased radiolucency was present in about half of the lung in 9 cases (Fig. 1)* and throughout the whole lung in 4 (Fig. 2). The pulmonary artery in the affected lung or lobe was decreased in size at its root. Its branches were reduced both in number and in size. When the whole pulmonary artery on one side was involved, the contralateral artery and its branches were enlarged (Fig. 2). The lung or lobe affected was reduced in size, as shown by the elevation of the dome of the diaphragm, displacement of the mediastinum towards the affected side, and by the position of the interlobar fissures. The diminished size of the pulmonary artery was evident on a plain P.A. radiograph, but tomography was useful in confirming this.

On fluoroscopy of the patients with the whole of one lung affected, the mediastinum was seen to swing away from the lesion during forced expiration. This was accompanied by an unusual increase in density of the vascular markings in the good lung. During forced inspiration, the mediastinum appeared to swing towards the lesion: this might have been merely the return of the mediastinum to its normal position after the preceding expiration. These changes in the position of the mediastinum were noted by Macleod (1954). When only a lobe was involved, it was more difficult to detect trapping, as this would have been masked by the normal lobe. Local air trapping may also be masked when there is generalised chronic bronchitis and emphysema.

BRONCHOGRAPHY

This was carried out on both sides in 11 cases, the only exceptions being 2 patients in whom the whole of the right lung was affected. In the majority

* The figure numbers in the text refer to Plates XXXVIII-XXXIX.

the bronchogram was abnormal, but this abnormality in most was not typical bronchiectasis.

In one case the bronchi in the affected right lower lobe and in the rest of the right lung were entirely normal. In the left lower lobe, where the arterial pattern was normal, there was mild dilatation of the peripheral parts of the basal bronchi. In another the bronchogram on both sides was normal. Minor to moderate tubular dilatation of lobar and segmental bronchi with poor filling of their smaller branches was observed in only 2 cases. Minimal dilatation of the periphery of the basal bronchi only was seen in one additional case.

Bronchial abnormalities of an unusual character were seen in 4 patients, consisting of small rounded areas in which pooling of contrast medium occurred. These " blobs " arose from the 4th to 6th order bronchi and were not confined to the radiolucent segment but were scattered throughout the lung (Fig. 3). The " blobs " varied in number and size and in one case only one large " blob " was present.

Crowding of lobar bronchi with very poor filling of their segmental branches, but without bronchial dilatation, was seen in 2 patients. In one case the only abnormality was a generalised reduction in the calibre of the bronchi, which had a " spidery " appearance. This feature was also seen in 2 of the cases described above in which " blobs " arose from minor bronchi.

Angiography

Little has been published on the normal size of the pulmonary arteries and their branches. In order to interpret the angiographic findings in our series of cases, measurements were made of the pulmonary arteries and their branches in a group of 52 patients who had had angiocardiograms and in whom there was no reason to believe that the size of the pulmonary vessels was affected by

Table IV.—Measurements of the Diameter (in mm.) of the Pulmonary Arteries
These were obtained from the angiocardiograms of 52 patients in whom there was no reason to expect that the pulmonary arteries were abnormal.

	P.T.	*R.P.A.*	*R.U.L.*	*R.L.L.(1)*	*R.L.L.(2)*	*L.P.A.*	*L.U.L.*	*L.L.L.(1)*	*L.L.L.(2)*
Number of cases	51	52	50	52	50	48	32	47	47
Maximum diameter	41	32	18	25	16	33	14	24	15
Minimum diameter	22	18	7	12	10	18	6	12	7
Mean diameter	30·77	24·6	12·25	19·1	12·76	24·77	10·4	17·72	11·22

disease. The points at which the arteries were measured on the angiograms are shown on Fig. 4 and the findings are recorded in Table IV. Measurements of the pulmonary arteries were also taken in 12 post-mortem specimens (Table V). It can be seen that there is a close correlation between the angiographic and post-mortem measurements of the pulmonary arteries in normal lungs.

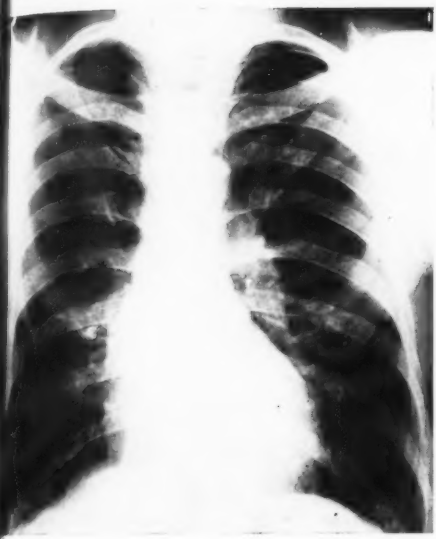

FIG. 1.—A radiograph showing increased radiolucency of the right lower lobe and a small lobar artery.

FIG. 2.—A radiograph showing increased radiolucency of the whole left lung. The left pulmonary artery is small and the right one large. (Film taken in expiration.)

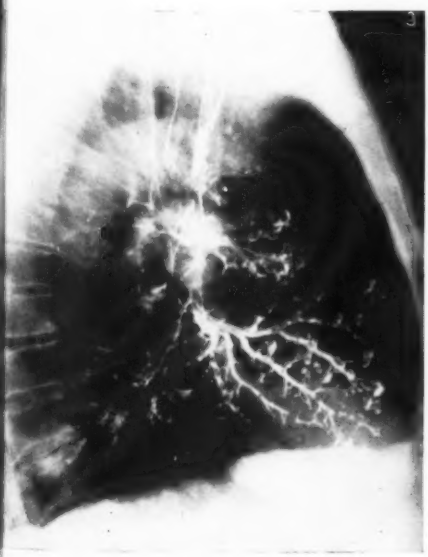

FIG. 3.—Case 1. A bronchogram showing scattered spherical dilatations of the peripheral bronchi throughout the whole right lung.

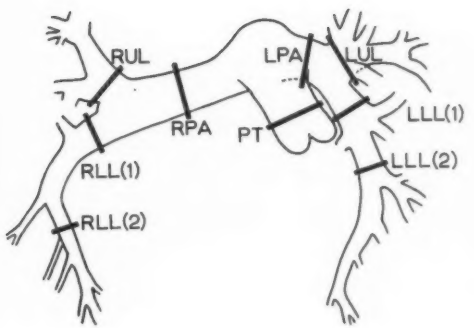

FIG. 4.—A diagram to show the points at which the measurements of the pulmonary arteries were made.

To face p. 25C

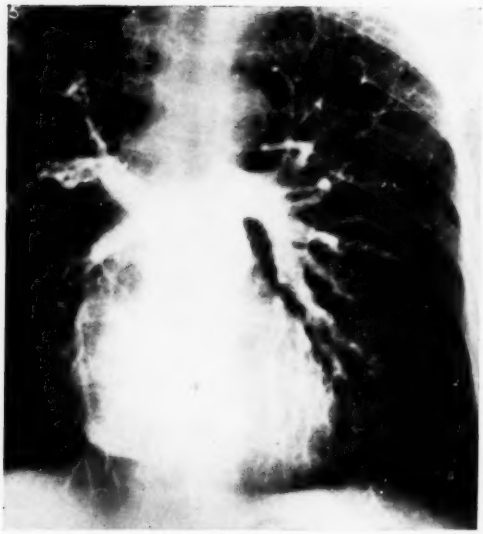

FIG. 5.—Case 7. An angiogram showing hypoplasia of the right lower lobe artery (6 mm.).

FIG. 6.—Case 11. An angiogram showing hypoplasi of the left pulmonary artery (14 mm. diameter), and a large right pulmonary artery (36 mm. diameter

FIG. 7.—Case 11. A radiograph in inspiration in a case with a small left pulmonary artery.

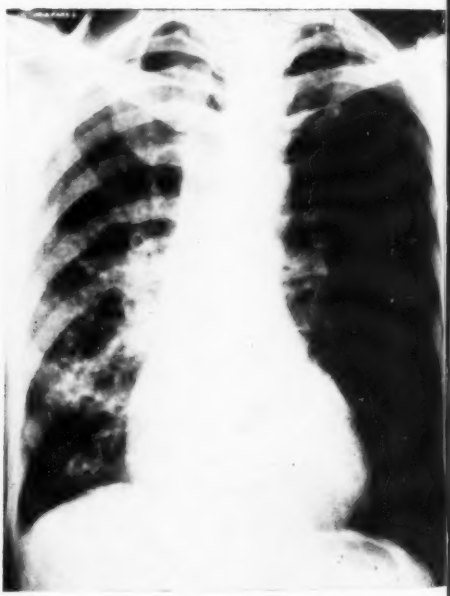

FIG. 8.—Case 11. A radiograph in expiration showing "trapping".

Allowances should be made for slight shrinkage after death and for a radiographic magnification of about 13 per cent. Since the external diameter of the arteries was measured at post-mortem and the internal diameter on the angiocardiogram films, the correction factors tend to cancel one another out. Angiography accurately depicts pulmonary artery size, for stream effects from inadequate mixing of contrast medium and blood do not occur with the intravenous or right atrial injection used in this series.

Angiograms were also done in 3 patients before operation for bronchiectasis. The lobar artery in the affected area was reduced in size on the angiogram, and here again the measurements corresponded closely with those on the specimen.

TABLE V.—PULMONARY ARTERY DIAMETERS

Post-mortem number	*Pulmonary trunk ext. diam. (mm.)*	*Right pul. artery ext. diam. (mm.)*	*Left pul. artery ext. diam. (mm.)*
371	37	25	27
372	32	20	22
373	30	20	22
376	28	20	20
377	29	21	19
380	30	24	22
386	27	19	18
388	31	23	25
390	32	21	20
392	34	26	25
378	28	21	18
379	35	26	22

	Max.	*Min.*	*Mean*
P.T.	37 mm.	27 mm.	31 mm.
L.P.A.	27 mm.	18 mm.	22·5 mm.
R.P.A.	26 mm.	19 mm.	22·2 mm.

Angiograms in several cases of emphysema were studied. The right and left pulmonary arteries were enlarged whilst their lobar branches gradually tapered down in size from their origins, which were more or less normal in diameter. The major abnormality was seen in the segmental and more peripheral arteries, which were much reduced in size and number.

Angiograms were obtained in 11 of our cases with hypoplasia of the pulmonary arteries, and measurements of the diameter of the pulmonary vessels taken at the points indicated in Fig. 4 are shown in Table VI. The affected artery was greatly reduced in size at its origin (Figs. 5 and 6) and its branches were reduced in size and number. In the affected area the circulation rate was invariably slower than normal, often markedly so. This phenomenon is also seen in emphysema and bronchiectasis.

TABLE VI.—DIAMETER OF THE HYPOPLASTIC PULMONARY ARTERIES COMPARED WITH THE CORRESPONDING ARTERY ON THE OPPOSITE SIDE. MEASUREMENTS OBTAINED FROM ANGIOGRAMS AND GIVEN IN MM.

Case number	*Artery to R.L.L.(2)*	*Artery to L.L.L.(2)*
1	5	14
2	12	6
3	6	10
4	9	20
5	6	15
6	13	7
7	6	14
8	10	15
9	5	11
	Right pulmonary artery	*Left pulmonary artery*
10	34	20
11	36	14
12	No angiogram	
13	No angiogram	

Average diameter of the nine hypoplastic lobar arteries = 6·7 mm.
Average diameter of the corresponding contralateral arteries = 13·8 mm.

LUNG FUNCTION STUDIES

Of the 9 patients with one lobe only involved, 5 were investigated by spirometry and bronchospirometry and 4 by fluoroscopy. Of the 4 patients with the whole of one lung involved, all were investigated by spirometry and fluoroscopy, and the 2 patients who later underwent pneumonectomy were also investigated by bronchospirometry. After operation their simple spirometry was repeated. The results are shown in Table VII.

The essential functional defect was a great reduction in oxygen uptake with marked, moderate or slight reduction in the tidal volume of the affected area when compared with the rest of the lung. These changes are also seen in bronchiectasis. These defects were revealed by bronchospirometry. In the 2 cases in which the whole of one lung was involved, and where therefore there was no contribution from a normal lobe to mask the defect, oxygen uptake was about 5 per cent. of the total, while the tidal volume was 13 per cent. and 23 per cent. of the total. Where only one lobe was affected, similar defects were present but partly masked by the contribution of the unaffected part of that lung. Tidal volume was reduced in all.

PATHOLOGY

Four specimens in all are available for histological study, 2 from this series and 2 from the series reported in 1957. The findings will be reported in detail by Dr. Lynne Reid in a separate publication.

TABLE VII.—LUNG FUNCTION STUDIES

Case number	*Lung zone affected*	*Trapping on fluoroscopy*	*Bronchospirometry*				*F.E.V.*	*F.E.R.*
			Oxygen uptake %	*Tidal volume %*	*V.C. %*	*Trap.*		
1	R.L.Z.	—	R. 22%	29%	R. 37%	+	1050	50
2	L.L.Z.	—	—	—	—	—	—	—
3	R.L.Z.	—	R. 39%	39%	R. 46%	0	1510	52
4	R.L.Z.	—	R. 30%	34%	R. 35%	0	1060	50
5	R.L.Z.	+ +	R. 5%	2%	R. 20%	+ + +	580	45
6	L.L.Z.	+ +	L. 40%	42%	L. 51%	+	2760	61
7	R.L.Z.	—	—	—	—	—	—	—
8	R.L.Z.	—	—	—	—	—	—	—
9	R.L.Z.	+ +	—	—	—	—	1030	60
10	L. lung	+ + +	L. 0 to 10	23%	L. 32%	+	1240	63
	Post-opn.						1230	61
11	L. lung	+ + +	L. 5%	13%	L. 26%	+ + +	1000	50
	Post-opn.						1000	50
12	R. lung	+ +	—	—	—	—	1600	67
13	L. lung	+ + +	—	—	—	—	1900	61

The Forced Expiratory Ratio (F.E.R. = one second forced expiratory volume as a percentage of forced vital capacity) is above 70 per cent in healthy people. When the F.E.R. is below 60 per cent., obstructive airway disease is usually present, and as its severity increases the F.E.R. drops towards 30 per cent (Capel and Smart, 1958). At bronchospirometry the tidal volume, oxygen uptake and vital capacity of the right lung is usually found to be 55 per cent. of the total in health.

Discussion

The 13 cases described here had certain radiological features in common: increased radiolucency of the whole or part of one lung, decrease in size of the affected segment and great reduction in size of the pulmonary arteries. They resemble the cases described by Macleod (1954), who commented on the paucity of vascular markings in his series.

Angiography, done in 11 of our 13 cases, showed a great reduction in the size and number of the pulmonary arteries and a diminished circulation rate in the affected area. The angiographic appearances differed from those seen in emphysema in that the affected pulmonary artery was small at its origin. In emphysema the pulmonary artery is often enlarged up to the origin of its lobar branches. The lobar arteries are more or less normal in diameter at their commencement and gradually taper off peripherally. The emphysematous lobe or lung is also increased in size.

The small size of the pulmonary artery is not a secondary change due to bronchiectasis, for the bronchogram was normal in 2 of our cases and bronchial dilatation was absent in another 2. The pulmonary artery supplying a grossly diseased lung undoubtedly becomes reduced in size, but seldom below 60 per cent. of its normal diameter (Björk and Salén, 1950). In our series of hypoplastic arteries the average diameter of the affected lobar arteries at their origin was 6·7 mm. while the corresponding contralateral vessels averaged 13·8 mm.

(Table VI). Such a prominent reduction in size (over 50 per cent.) is seldom seen even in severe bronchiectasis.

A diminution in the size and number of the peripheral pulmonary arteries is seen in primary and secondary pulmonary hypertension. These changes, however, are bilateral and the reduction in calibre occurs distal to the second subdivision of the artery. The main pulmonary arteries and their lobar branches are enlarged (Goodwin, Steiner and Lowe, 1952). Similar changes may be produced by multiple peripheral emboli or thromboses. The angiographic appearances in these conditions are quite different from those seen in our cases.

We suggested in a previous paper (Belcher and Pattinson, 1956) that a congenital origin was the most likely cause of the arterial hypoplasia and that infection and bonchiectasis might be complicating factors. Since congenital absence of the pulmonary artery to one lung may occur (Madoff and others, 1952; Emanuel and Pattinson, 1956), it is probable that congenitally small arteries also exist. When one pulmonary artery is congenitally absent, the affected lung is small. Diminished size of that portion of the lung supplied by the hypoplastic artery was a constant feature in our cases. A congenital defect in the form of abnormal interlobar fissures was seen in 2 of our previously reported cases. In our cases in which the whole of the pulmonary artery on one side was small, the contralateral artery was enlarged (Fig. 6), suggesting that the hypoplasia was at least of long-standing. Such enlargement is seldom seen even many years after pulmonary resection in children, and even then not to a marked degree.

Smart and Pattinson (1956) reported a case of congenital absence of the left pulmonary artery. Oxygen uptake by the left lung was nil, while the tidal volume was only slightly reduced. Similar results were obtained in 3 other unpublished cases. Therefore complete absence of a pulmonary artery will not of itself necessarily cause a ventilatory defect. In one patient previously reported (Case 3 in 1957) there was a marked loss of oxygen uptake in the presence of a normal tidal volume. In such cases the lesion may be solely congenital in origin.

When both ventilation and oxygen uptake are defective, the lesion may be due to an acquired ventilatory defect complicating a congenital arterial anomaly, but the possibility that the lesion is entirely acquired cannot be excluded. The abnormality in some cases might be due to lung damage suffered during the growing period. This possibility is favoured by the relative frequency with which serious chest illness in childhood has been reported in this condition (Table VIII). The strongest argument against a congenital ætiology is that the condition has never been reported in infancy. Hypoplasia of the artery, however, is not in itself responsible for symptoms, and the abnormality may easily be overlooked on a chest radiograph. In several of our cases the appearances on previous radiographs had been ignored or misinterpreted. It is also very probable that the small size of the arteries will be missed at routine post-mortem, particularly when lobar arteries alone are involved.

Symptoms due to secondary or unrelated pulmonary disease frequently

appear for the first time in men between the ages of 40 and 50 years. As a result, most of our patients and those in other reported series were men in their early forties who presented with a variety of chest complaints (Table III). Although the abnormal lobe or lung in itself causes no symptoms, the respiratory reserve is diminished, for the affected area takes up little oxygen (Table VII). Thus the respiratory effort required to fill the useless part of the lung is wasted. If then the respiratory reserve in the rest of the lungs becomes reduced from whatever cause (such as chronic bronchitis), the presence of the abnormality will contribute indirectly to the breathlessness. It will do so not only because of the loss of respiratory reserve, but also because in some cases it may diminish the ventilation of the other lung. It may do this if air trapping during exercise causes a mediastinal shift towards the normal lung (Figs. 7 and 8). Trapping was present in each of the 4 patients with the whole of the right or left pulmonary

TABLE VIII.—INCIDENCE OF SEVERE ILLNESS IN CHILDHOOD IN 43 PATIENTS WITH UNILATERAL HYPOPLASIA OF A PULMONARY ARTERY, OF WHOM 26 WERE QUESTIONED, AND IN 74 CHEST HOSPITAL OUT-PATIENTS SUFFERING FROM CHRONIC BRONCHITIS AND EMPHYSEMA OR PULMONARY TUBERCULOSIS

Author	*No. reported*	*No. questioned*	*Childhood illness*
Swyer and James ..	1	1	1
Macleod	13	4	4
Belcher and Pattinson ..	3	1	0
Dornhorst *et al.*	4	4	2
Ogilvie	7	7	6
Present series	15	9	4
Total	43	26	17
Control series	74	74	11

artery affected. The forced expiratory spirogram is sometimes characteristic: a sharp descent as the healthy lung empties, followed by an unusually sharp deflection as air trapped in the abnormal lung interferes with further emptying of the healthy lung and slowly makes its own contribution. This interference may be critical if the other lung is affected by airway disease such as chronic bronchitis and emphysema.

Whatever the cause of the lesion, the presence of a hypoplastic pulmonary artery is of practical importance. Some patients are symptom free and may never develop respiratory distress. The onset of inflammatory or neoplastic processes in the only functioning lung is of much graver import than in the average patient and requires prompt treatment. Coexisting bronchiectasis can be treated on its merits, bearing in mind that one area of lung (which may or may not be the segment most severely affected by the bronchiectasis) is almost functionless because of the arterial hypoplasia.

If there is effort intolerance (the patient is unable to maintain normal walking pace) and severe trapping in the abnormal lung, then pneumonectomy

may help. This was carried out in 2 of our patients. The improvement in Case 11 was great while in Case 10 it was slight. In neither case was there any significant change in the spirometry findings after pneumonectomy. This reflects the severe ventilatory defect of the removed lung.

The diagnosis of the condition is essentially radiological. The presence of hypoplasia of the pulmonary artery should be suspected whenever a lobe or lung shows increased radiolucency and diminished size. A close study of the vascular pattern on the P.A. chest film will usually establish the diagnosis. Angiography is helpful in doubtful cases, especially if there is difficulty in distinguishing between hypoplasia and congenital absence of the artery to one lung, although in practice the functional difference is often slight.

Summary

1. Thirteen new cases of unilateral increased radiolucency of the lung (Macleod's syndrome) are reported.

2. Bronchography, bronchospirometry and angiography were carried out in the majority of the cases.

3. All cases were shown to have small pulmonary arteries in the affected area. In 9, lobar arteries were involved, and in 4 the whole artery on one side was affected.

4. In 2 cases the bronchogram was normal. In the remainder the abnormality was not that of typical bronchiectasis.

5. Bronchospirometry showed that the oxygen uptake was reduced considerably more than the ventilation on the affected side.

6. The ætiology is discussed. It is thought that the condition may be congenital in origin or that it may be acquired during the growing period.

7. The abnormality does not cause symptoms but it may aggravate breathlessness due to disease in the unaffected lung.

8. The practical significance of the anomaly and its treatment are discussed.

We thank our colleagues who have referred cases to us.

REFERENCES

BELCHER, J. R., and PATTINSON, J. N. (1957): *J. thorac. Surg.*, **34**, 357.
BJÖRK, V. O., and SALÉN, E. F. (1950): *J. thorac. Surg.*, **20**, 933.
CAPEL, L., and SMART, J. (1958): *Lancet*, **2**, 771.
DORNHORST, A. C., HEAF, P. J., and SEMPLE, S. J. (1957): *Lancet*, **2**, 873.
EMANUEL, R., and PATTINSON, J. N. (1956): *Brit. Heart J.*, **18**, 289.
GOODWIN, J. F., STEINER, R. E., and LOWE, K. G. (1952): *J. Fac. Radiol. (Lond.)*, **4**, 21.
MADOFF, I. M., GAENSLER, E. A., and STREIDER, J. W. (1952): *New Engl. J. Med.*, **247**, 149.
MACLEOD, W. M. (1954): *Thorax*, **9**, 147.
OGILVIE, C. M. (1959): Personal communication.
SHAPIRO, R., and RIGLER, L. G. (1948): *Amer. J. Roentgenol.*, **60**, 460.
SMART, J., and PATTINSON, J. N. (1956): *Brit. med. J.*, **1**, 491.
SWYER, P. R., and JAMES, C. W. (1953): *Thorax*, **8**, 133.

Brit. J. Dis. Chest (1959) **53**, 263.

PATENT DUCTUS ARTERIOSUS IN ADULT LIFE

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During the last ten years much has been written on the subject of patent ductus arteriosus and several large series have been published (Gross, 1952; Campbell, 1955; Wood, 1956; Cosh, 1957). These have included patients of all ages, and relatively little has been written about the problems of patent ductus in adult life. The purpose of this paper is to draw attention to these problems, and to emphasise the beneficial and dramatic results of surgical treatment in those patients with a left-to-right (aorto-pulmonary) shunt who comprise the majority of the cases.

Present Series

This consists of 43 patients over the age of 20 with patent ductus arteriosus, who have been admitted to Hammersmith and St. Bartholomew's Hospitals during the past ten years.

There were 31 women and 12 men, giving a male : female ratio of 2·6 : 1, which is similar to previous reports with ratios of 2·3 : 1 (Gross, 1952) and 2·7 : 1 (Campbell, 1955; Cosh, 1957).

The age, at the time of first admission to hospital, varied from 21-66 years, and the distribution in each decade is represented in Table I.

Table I.—Age on First Admission of 43 Adult Patients with a Patent Ductus

Age in decades	*No. males*	*No. females*	%
21-30 ..	6	12	42
31-40 ..	3	8	25
41-50 ..	3	6	21
51-60 ..	0	3	7
61-70 ..	0	2	5
Total ..	12 +	31 =	43

It is interesting that there were no men over the age of 50. The 4 oldest patients on record, aged 85 (Bain, 1957), 79 (Holman *et al.*, 1953), 75 (Fishman and Silverthorne, 1951) and 72 (Storstein *et al.*, 1952), were all women. In

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Campbell's series (Campbell, 1955) the oldest man was 44, and there were 5 women over the age of 44. In this series there are 3 patients over the age of 60, all of whom are women.

We have divided the patients into two groups: A, with a left-to-right shunt; B with a right-to-left shunt due to extreme pulmonary hypertension (Eisenmenger syndrome) (Wood, 1956, 1958). This has been done because the clinical features, treatment and prognosis differ markedly in the two groups.

A—Patent Ductus Arteriosus with a Left-to-Right Shunt

There were 40 patients in this group, representing 93 per cent. of the total. This incidence is similar to the findings of Wood (1956). The diagnosis has been established by thoracotomy or by cardiac catheterisation in all patients.

Assessment at the Time of First Admission to Hospital

Symptoms

Symptoms present at the time of first admission to hospital are shown in Table II. The commonest complaint was of breathlessness, which was present in 24 patients and which ranged in severity from mild to very severe. All the patients over the age of 40, and 12 out of 28 under the age of 40, suffered from dyspnœa when they were first seen. These figures are slightly misleading as the age of onset of symptoms varies. Of the 28 patients with symptoms 16 had developed these by the age of 30, while 2 patients were asymptomatic until the ages of 58 and 61 respectively. Gross (1952) and Campbell (1955) also stress that many patients are asymptomatic till middle life or later.

Table II.—Symptoms on First Admission of 40 Adult Patients with a Patent Ductus and a Left-to-Right Shunt

Symptom	*No. cases*	*Per cent.*
Dyspnœa on exertion	24	60
Completely symptomless	12	30
Left submammary pain	10	25
Palpitations	6	15
Cough with sputum	5	12·5
Angina pectoris	3	7·5
Hæmoptysis	2	5
Lassitude	2	5

Ten patients had left submammary pain and 3 had classical angina pectoris. The diagnosis of angina was made in those patients with central chest pain occurring only on exertion and always relieved by rest within a few minutes. Angina does not appear to have been stressed previously, although præcordial pain is mentioned as a symptom by Kuhn (1958), who states that it is much commoner in the patients with pulmonary hypertension and a reversed shunt.

The other symptoms included palpitations, bronchitis (cough with sputum), hæmoptysis and lassitude. The 12 patients who were symptomless were referred because a murmur had been discovered during the course of a routine medical examination.

Signs

Arterial Pulse—Rhythm. Thirty-six patients (90 per cent.) were in sinus rhythm, and the remaining 4 (10 per cent.) had atrial fibrillation.

Character. Thirty-four patients (85 per cent.) had a collapsing pulse, and in the remainder the pulse was normal.

Blood Pressure. There was a wide variation in blood pressure with diastolic pressures ranging from 35 to 90, systolic from 110 to 240 and pulse pressures from 40 to 150 mm. Hg. The most frequent feature was the depression of the diastolic pressure, which invariably rose following closure of the duct (Fig. 1).*

Heart—Continuous Murmur. The classical continuous murmur of Gibson (1900) was heard in 39 patients (97·5 per cent.). This is in accordance with the findings of others (Campbell, 1955; Gross, 1952; Wood, 1956). The one exception in our series is a patient with a re-canalised duct, which was closed while infected. This patient has a pulmonary systolic and diastolic murmur, but these are not continuous.

Apical Mid-diastolic Murmur. This was present in 9 patients (23 per cent.), indicating a greatly increased blood flow through the mitral valve due to a large shunt. There was supporting evidence of a considerable shunt from the symptoms, heart size, enlargement of the left atrium, and cardiographic changes of left ventricular hypertrophy in these patients. Cardiac catheterisation, when performed, confirmed this, and in one case the shunt was 24·7 litres/minute, giving a pulmonary : systemic flow ratio of 5·6 : 1.

Other Murmurs—Mitral systolic Murmur. This was present in 3 patients and was thought to be due to functional mitral incompetence resulting from left ventricular failure.

Pulmonary Murmurs. These were present in 4 patients (10 per cent.). In one patient in whom the duct had re-canalised, as already stated, the classical Gibson murmur was replaced by pulmonary systolic and early diastolic murmurs. In another patient, in addition to the classical continuous murmur, there was a pulmonary ejection click followed by an ejection systolic murmur, associated with gross dilatation of the main pulmonary artery. In this patient the pulmonary arteriolar resistance was elevated to 5 units. In the remaining 2 patients pulmonary systolic and diastolic murmurs were heard as well as the continuous murmur and again there was gross dilatation of the main pulmonary artery.

Aortic Murmurs. These were present in 2 patients (5 per cent.) The first had suffered from rheumatic fever and had both systolic and diastolic aortic murmurs, which persisted after operation, and were presumably caused by a rheumatic lesion of the aortic valve. The second patient had a soft aortic ejection murmur in addition to the continuous duct murmur.

* The figure numbers in the text refer to Plates XL-XLIII.

Cardiography

Satisfactory cardiograms were available in 36 out of 40 patients in this group. Twenty-seven patients (77 per cent.) had evidence of left ventricular hypertrophy. This was expressed in four grades as used by Fleming and Gibson (1957), and 16 patients had Grade I changes, 7 patients Grade II, 3 patients Grade III, and 1 patient Grade IV changes (Fig. 2). Two patients also had right ventricular hypertrophy. Left atrial hypertrophy was present in 3 patients.

Left ventricular hypertrophy and, in the severe cases, left atrial hypertrophy were to be expected. Right ventricular hypertrophy was considered to be due to pulmonary hypertension, although pulmonary stenosis was not excluded with certainty as cardiac catheterisation was not performed on these 2 patients.

Ischæmic Changes. Effort tests were carried out on 5 patients, all of whom suffered from dyspnœa, and 3 from angina pectoris.

In the patients with angina there were slight but inconclusive changes suggestive of ischaemia on exertion, and the tests were therefore regarded as negative. However, in one patient, a man aged 30 who did not suffer from angina, a strongly positive test was obtained (Fig. 3).

It was extremely difficult to assess changes due to ischæmia in many of these patients because of the ST depression due to left ventricular hypertrophy.

Radiography

Six-foot postero-anterior chest radiographs taken at the time of first admission were available in 24 patients. These showed that there was cardiac enlargement in 14 patients (58 per cent.), the criterion for an increase in size being a cardiac-thoracic ratio of more than 50 per cent.

In all twenty-four radiographs the main pulmonary artery was enlarged, and this was also reported in a further eight films which were not available for inspection. Radiological evidence of a dilated main pulmonary artery was therefore an invariable finding, not only in this group but also in those with the Eisenmenger reaction.

In all patients except those with very small shunts there was also pulmonary plethora with dilatation of the more peripheral pulmonary arteries. This is in marked contrast to the Eisenmenger group, in which the peripheral branches of the pulmonary artery were narrowed.

Films demonstrating the size of the left atrium were not available in enough patients to make any conclusions reliable. However, of fourteen cases with lateral or oblique radiographs with a barium swallow, the left atrium was enlarged in nine, and of these six also had a mitral diastolic murmur indicating the presence of a considerable shunt.

The patients with a moderate or large shunt also had radiological evidence of left ventricular enlargement. Although the aortic knuckle was frequently enlarged, the angle between it and the main pulmonary artery was preserved. This is in contrast to children, in whom this angle is often obliterated owing to the presence of the duct.

Cardiac Catheterisation

Seventeen of the forty patients were catheterised.

Pulmonary Arterial Pressure. The systolic pressure varied from 18 to 100 mm. Hg and the diastolic from 7 to 55 mm. Hg. The pressure was raised in 9 patients (the upper limit of normal being 30/15 mm. Hg). The range in our patients is slightly wider than in the series of Wood (1956), whose figures varied from 32/15 to 75/55 mm. Hg (Table III).

TABLE III.—PULMONARY ARTERIAL PRESSURES IN 17 PATIENTS WITH A PATENT DUCTUS AND A LEFT-TO-RIGHT SHUNT

Age	*Sex*	*Systolic pressure (mm. Hg)*	*Diastolic pressure (mm. Hg)*	*Mean pressure (mm. Hg)*
66	F	38	28	31
63	F	100	25	40
49	F	39	31	33
43	M	25	14	17
42	F	25	7	13
42	M	—	—	18
41	F	30	14	22
40	M	18	10	13
37	M	—	—	54
35	F	—	—	55
34	F	90	50	63
31	M	60	—	—
30	F	70	55	60
29	M	20	5	10
25	F	—	—	22
25	M	—	—	34
21	M	—	—	16

Pulmonary Vascular Resistance. The pulmonary arteriolar resistance was elevated in only one case in which it was measured, being 5 units. The majority of the patients in this series were catheterised before routine wedge pressures and estimations of cardiac output were being made, and therefore we have only been able to calculate the total pulmonary resistance. The total pulmonary resistance was normal (below 4 units) in 8 out of 9 patients, and was elevated to 6 units in one patient only.

The pulmonary resistance may remain normal for many years despite a greatly increased pulmonary blood flow, and there was no tendency for the pulmonary resistance to rise with increasing age (Fig. 4).

Shunts. The left-to-right shunts varied from 3 to 25 litres/minute, giving ratios of pulmonary : systemic flow varying from 1·5 to 5·6 : 1.

Complications

1. *Subacute bacterial endocarditis* was present in 4 patients (10 per cent.). This is similar to the findings of Cosh (1957), who studied a series of 73 cases in

which 6 had bacterial endocarditis (8 per cent.) and who calculated that the incidence was 0·4 per cent./annum.

2. *Congestive cardiac failure* as judged by elevation of the venous pressure, enlargement of the liver, peripheral œdema, crepitations in the lungs and radiological evidence of pulmonary venous congestion with or without pulmonary œdema was present in 3 patients (7·5 per cent). The patients were women aged 48, 49 and 66, all of whom were dramatically improved by closure of the duct.

Treatment and Progress

Since ligation of a patent ductus was first recorded by Gross and Hubbard (1939), many patients have received surgical treatment. In this series 36 out of 40 patients with a left-to-right shunt were treated surgically.

Results of Surgical Treatment

Symptoms. There was a marked improvement in symptoms in most patients (Table IV). Twenty-four patients had symptoms before operation, and of these 13 became symptom-free, 10 were improved and 1 was unchanged following closure of the duct. Twelve patients were symptomless before operation and of these 11 remained so, while 1 developed dyspnœa on exertion, after closure of the duct.

TABLE IV.—SYMPTOMATIC IMPROVEMENT FOLLOWING CLOSURE OF A PATENT DUCTUS IN 36 ADULT PATIENTS

Symptom	*No. cases*	
	Before operation	*After operation*
Dyspnœa on exertion	20	10
Completely symptomless	12	24
Left submammary pain	7	0
Palpitations	5	2
Cough with sputum	4	0
Angina pectoris	3	0
Hæmoptysis	1	0
Lassitude	2	2

The patient who developed dyspnœa following the operation was a woman aged 33 with marked pulmonary hypertension, the pulmonary pressure being 70/55 mm. Hg, with a pulmonary arteriolar resistance of 5 units and a left-to-right shunt of 5·8 litres/minute. The total pulmonary resistance was 6 units. It is possible that, despite closure of the duct and the subsequent reduction in pulmonary blood flow, the pulmonary pressure and resistance have remained elevated, for there is no evidence of any other cardiac lesion. The fact that a loud pulmonary second sound, an ejection click and systolic murmur

are still present in this patient after operation favours the persistence of pulmonary hypertension, but the click and murmur could be due to enlargement of the pulmonary artery.

As a result of surgical treatment the number of symptomless patients has been doubled and the number with dyspnœa halved. Although 10 patients still complained of dyspnœa after the operation, there was a marked improvement in effort tolerance. The effort tolerance, as judged by dyspnœa in the 36 patients before and after operation, is shown in Fig. 5. Dyspnœa is represented by 4 grades of severity as used by Wood (1956). Left submammary pain, angina pectoris, cough with sputum, and hæmoptysis were abolished and the number of patients with palpitations reduced from 5 to 2. The 2 patients who complained of tiredness continue to do so.

Signs

Pulse—Rhythm. Of the 4 patients with atrial fibrillation 3 received surgical treatment. The fibrillation persisted in 2 patients, while the third who had developed it shortly before operation was restored to sinus rhythm postoperatively with quinidine. Of the 33 patients with sinus rhythm, 31 remained so and 2 had transient atrial fibrillation during or after operation, but they both reverted to a sinus rhythm either spontaneously or with quinidine.

Blood Pressure. A rise in diastolic pressure is well known to follow ligation of a patent ductus (Gross, 1943 and 1952; Tubbs, 1944) and this is demonstrated in Fig. 1 showing the diastolic pressure before and after operation in each of the 36 patients. The pressure rose in every case, the increase varying from 5 to 40 mm. Hg.

Heart: Continuous Murmur. This disappeared in every patient.

Apical Mid-diastolic Murmur. There were 8 patients with this murmur before operation and in all it was abolished.

Mitral Systolic Murmur. This was heard in 2 patients with evidence of cardiac failure before operation but was not present after operation.

Pulmonary Murmurs. A pulmonary diastolic murmur was present in 2 cases before operation and it persisted afterwards.

A pulmonary systolic murmur was recognised in 3 patients before operation and in 13 patients after operation. The presence of the continuous murmur before ligation was probably masking a soft pulmonary ejection murmur. The patient whose duct was closed while infected developed pulmonary systolic and diastolic murmurs at a later date when the duct was found on cardiac catheterisation to have re-canalised.

Aortic Murmurs. These were unaffected by closure of the duct in the 2 patients in whom they were present.

Cardiographic Changes

Marked degrees of left ventricular hypertrophy regressed but mild degrees persisted.

X-ray Changes

In 17 patients strictly comparable 6-foot postero-anterior chest radiographs were available for assessment of heart size before and after operation. In only 2 patients was the heart size unchanged. In the remainder there was a reduction in the transverse diameter of the heart, ranging from 0·5 to 3 cm. (Figs. 6, 7 and 8).

The other changes noted were the disappearance of pulmonary plethora, a decrease in the size of the main pulmonary artery, and a reduction in the size of the left atrium and left ventricle.

Complications

There were no deaths as a result of surgery, despite the fact that the oldest patient was 66 at the time of operation. In one case the rare complication of re-canalisation occurred and this was in a patient whose duct was ligated in 1943 while it was still infected.

Case Reports

Two patients deserve special mention because they illustrate the marked improvement which may follow closure of a duct even in elderly people, and demonstrate that a patient may have a large left-to-right shunt for many years without developing a raised pulmonary vascular resistance. Case 1 is particularly interesting as the onset of symptoms was delayed until the age of 61, and also because she appears to be the oldest patient yet to have had surgical treatment.

Case 1. A woman, aged 66, was admitted to St. Bartholomew's Hospital under the care of Dr. Geoffrey Bourne in 1957. She said that up to the age of 61 she had been free from symptoms, but during the next five years she suffered from increasing dyspnœa, palpitations and left submammary pain. At the time of admission she was severely incapacitated with dyspnœa of Grade III severity.

On examination she looked ill. She was in sinus rhythm with a markedly collapsing pulse and a blood pressure of 160/60. The heart was enlarged with a strong left ventricular impulse, and she had the classical continuous murmur, together with pulmonary systolic and diastolic murmurs. She also had evidence of congestive cardiac failure with a raised jugular venous pressure, enlarged liver, crepitations at the base of the lungs, but no peripheral œdema.

The electrocardiogram showed evidence of left ventricular hypertrophy (Grade II) but no other abnormality.

The chest X-ray showed considerable cardiac enlargement, the transverse diameter of the heart being 17 cm., with a cardiac : thoracic ratio of 71 per cent. The main pulmonary artery was enlarged and there was marked pulmonary plethora. The aortic knuckle was prominent and calcified (Fig. 7).

Cardiac catheterisation was performed and demonstrated the presence of a left-to-right (aorto-pulmonary) shunt of 4·2 litres/minute, giving a pulmonary : systemic flow ratio of 2 : 1. The pulmonary pressure was elevated at 38/28 mm. Hg with a pulmonary arteriolar resistance of 2 units and total pulmonary resistance of 3 units. Shortly before operation she developed atrial fibrillation, but sinus rhythm was restored on the twenty-eighth post-operative day with quinidine.

On 14.10.57 the duct was closed by ligation and division by Mr. O. S.

Tubbs, with dramatic improvement. The dyspnœa was considerably relieved, the diastolic pressure rose from 60 to 90 mm. Hg and the heart was reduced in size from 17 to 15 cm. diameter with a reduction in cardiac: thoracic ratio from 71 to 62 per cent. This change in heart size occurred soon after operation and Fig. 7 (*b*) shows a radiograph taken five weeks after the operation. The pulmonary plethora has disappeared and the main pulmonary artery is reduced in size. The only abnormal signs remaining were pulmonary systolic and diastolic murmurs, together with some residual cardiac enlargement. There is no evidence of congestive cardiac failure at present.

Case 2. A woman, aged 49, was admitted to Hammersmith Hospital. She gave a past history of rheumatic fever and for at least ten years had suffered from moderate exertional dyspnœa (Grade II (b)).

On examination she had atrial fibrillation with a marked collapsing pulse. The blood pressure was 130/60. There was cardiac enlargement with a strong left ventricular impulse, together with accentuation of the pulmonary component of the second heart sound, a continuous murmur, a mitral diastolic murmur at the apex, and both systolic and diastolic aortic murmurs. There was evidence of congestive cardiac failure and tricuspid incompetence with an elevated jugular venous pressure (8 cm. above the sternal angle), with a marked systolic expansile pulsation (" cv " wave), an enlarged pulsating liver, and crepitations at the base of the lungs.

The cardiogram showed evidence of left ventricular hypertrophy (Grade III) and atrial fibrillation but no other abnormality.

The chest radiograph showed cardiac enlargement with a transverse diameter of 17·5 cm., giving a cardiac : thoracic ratio of 80 per cent. All the chambers were enlarged, particularly the left atrium and left ventricle, and there was also enlargement of both the aorta and the main pulmonary artery. Pulmonary plethora was present as well as evidence of venous hypertension (Fig. 8).

Cardiac catheterisation showed the presence of a very large pulmonary blood flow (30 litres/minute) giving a pulmonary : systemic flow ratio of 5·6 : 1. The pulmonary arterial pressure was 39/31 mm. Hg and the pulmonary capillary pressure 14 mm. Hg (mean). The arteriolar resistance was normal at 0·6 unit. (The total pulmonary resistance was 1 unit.)

The duct was closed by Mr. W. P. Cleland, who also explored the mitral valve, which was found to be normal. After the operation there was considerable improvement and now breathlessness occurs only on marked exertion (Grade I). The diastolic pressure rose from 60-80 mm. Hg and the heart was reduced in size from 17·5 to 14·5 cm. (Fig. 8). The cardiogram remained unchanged, as did the early diastolic murmur. It was concluded that this patient had chronic rheumatic aortic valvular disease as well as a patent ductus, although pulmonary incompetence could not be excluded.

The 4 patients who were not treated surgically have remained unchanged for variable periods of up to seven years.

B—Patent Ductus Arteriosus with a Right-to-Left Shunt due to Pulmonary Hypertension (Eisenmenger Reaction)

There were 3 patients in this group representing 7·5 per cent. of the total. The difference between these patients and the previous group with a left-to-

right shunt have been stressed many times (Johnson *et al.*, 1950; Campbell and Hudson, 1951; Bothwell *et al.*, 1952; Dammann and Sell, 1952; Cosh, 1953; Hultgren *et al.*, 1953; Smith, 1954; Campbell, 1955; Harris, 1955; Whittaker *et al.*, 1955; Ellis *et al.*, 1956; Wood, 1956; Kuhn, 1958; Wood, 1958) and are well illustrated by our patients.

Symptoms

There were two men aged 42 and 48 and one woman of 30. They all complained of exertional dyspnœa (Grade II (b)) which had been present for many years, and in addition one man had chronic bronchitis, gout and was said to have been cyanosed from early childhood.

Signs

Pulse and Blood Pressure. There was sinus rhythm in all 3 cases, and the pulse was of normal form but small volume. There was no widening of the pulse pressure with a low diastolic pressure as in the previous group, and the blood pressures varied from 110/60 to 140/100.

Heart. There was a right ventricular cardiac impulse, in contrast to the left ventricular impulse in patients with a left-to-right shunt. There was narrow splitting of the second heart sound with marked accentuation of the pulmonary component. A pulmonary systolic ejection murmur was heard, and in 1 case a pulmonary diastolic murmur was present. In no case was there a continuous murmur.

Cyanosis. All 3 cases were cyanosed but only in 1 patient was there obvious differential cyanosis, the toes being cyanosed but not the fingers. Part of the cyanosis in these patients was peripheral and due to a diminished cardiac output associated with pulmonary hypertension, and part was central, due to the shunt.

Cardiography

This confirmed the clinical impression of right rather than left ventricular hypertrophy in all 3 patients and there was a partial right bundle branch block pattern in one patient.

Radiography

As with the first group the main pulmonary artery was prominent, but the peripheral vessels instead of being dilated were narrowed at the extreme periphery in all zones. The right ventricle was enlarged and the aorta slightly prominent.

Cardiac Catheterisation

This was carried out in all 3 patients and demonstrated balanced pulmonary and systemic arterial pressures, and a variable right-to-left shunt. The pul-

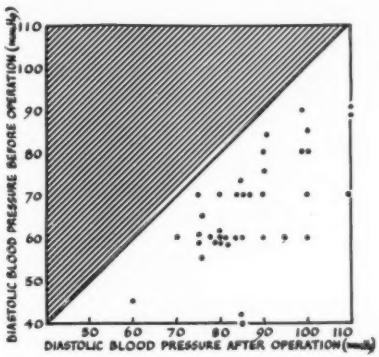

FIG. 1.—Diastolic blood pressure before and after closure of patent ductus in 36 adult patients.

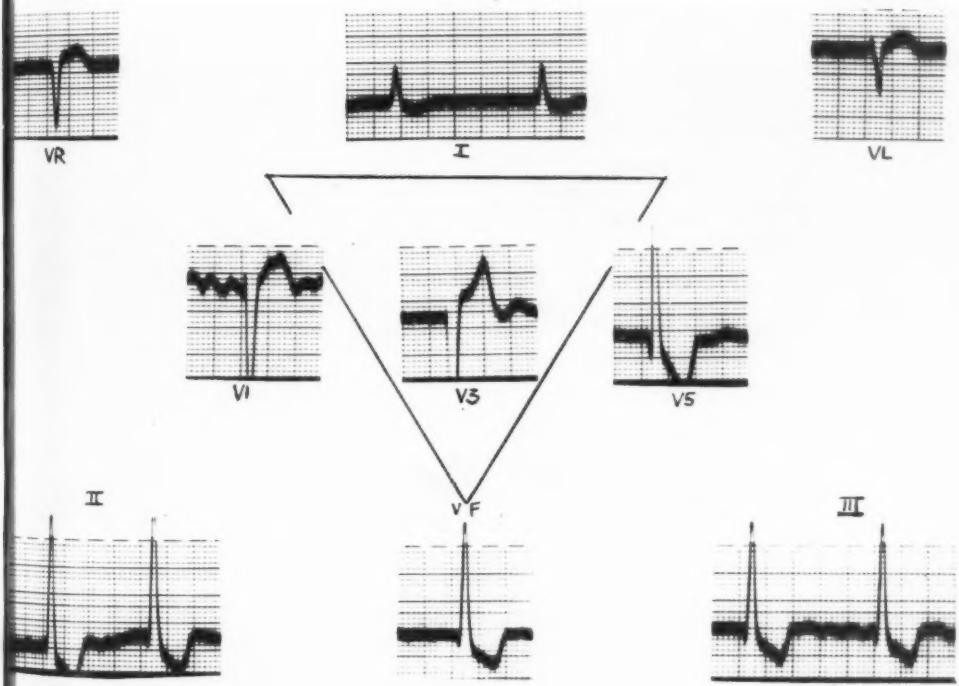

FIG. 2.—The cardiogram of a woman aged 35 with a patent ductus showing artial fibrillation, left ventricular hypertrophy, and a vertical position of the heart probably due to associated right ventricular enlargement.

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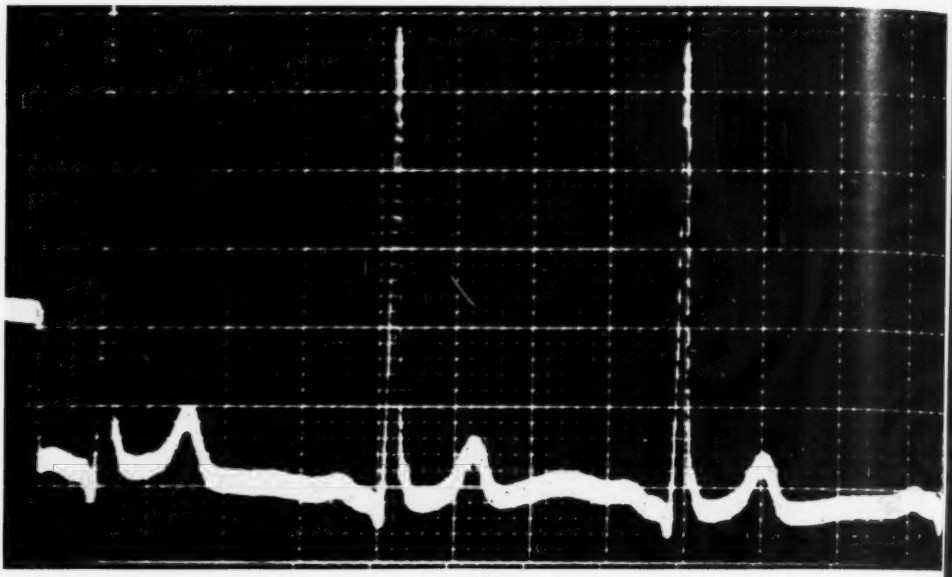
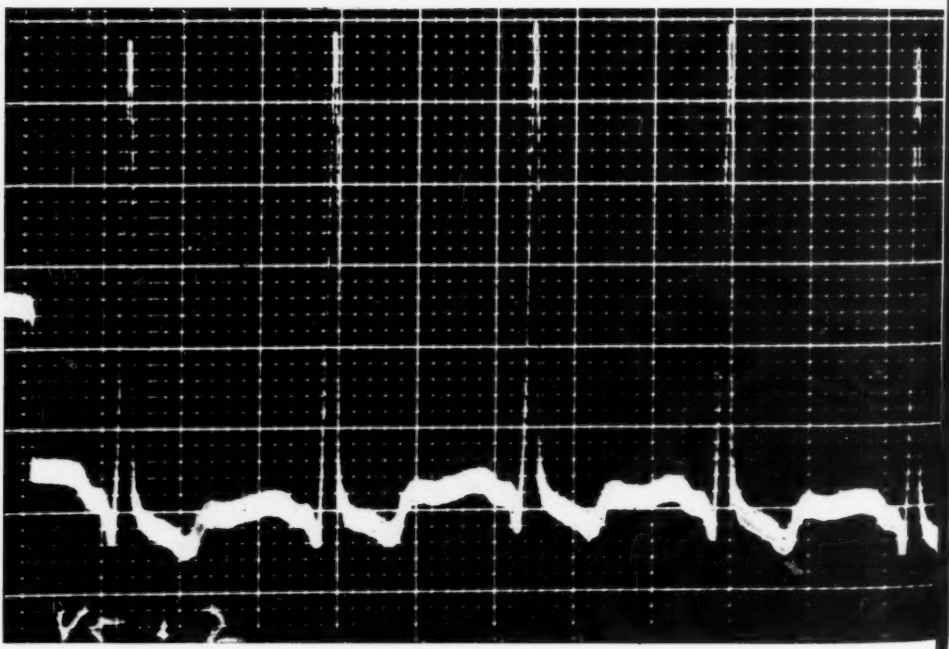


(A)



(B)

FIG. 3.—Lead V_5 of a cardiogram taken (A) before and (B) 2 minutes after exercise in a man aged 30 with a patent ductus. The T wave inversion after exercise indicates ischaemia. (Positive effort test.)

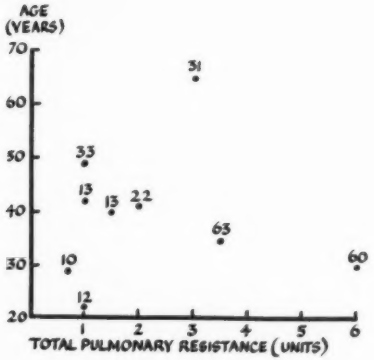


FIG. 4.—Age and total pulmonary vascular resistance in 9 patients with patent ductus. (The figure above each spot indicates the mean pulmonary arterial pressure in mm.Hg.)

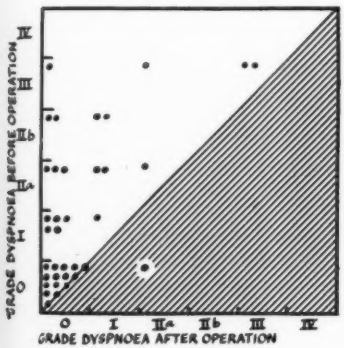


FIG. 5.—Severity of dyspnœa before and after closure of patent ductus in 36 adults.

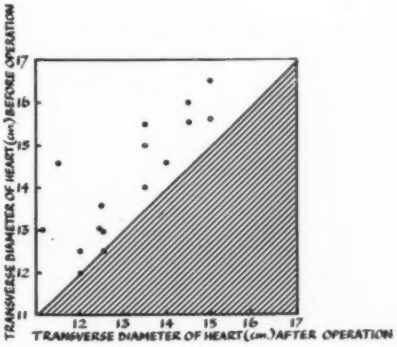
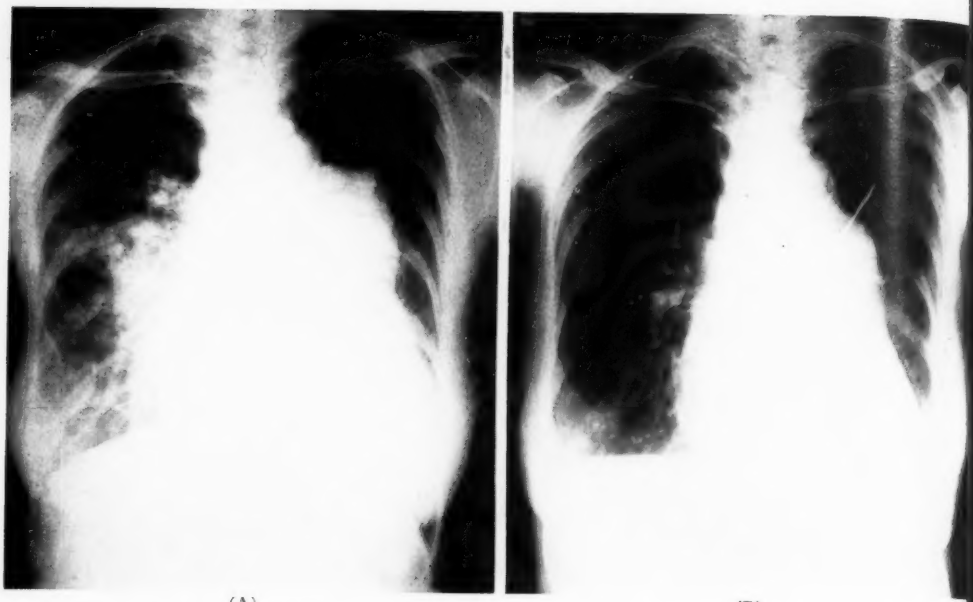


FIG. 6.—Transverse diameter of the heart on X-ray before and after closure of patent ductus in 17 adult patients.



(A) (B)

FIG. 7.—6 ft. postero-anterior chest radiographs (A) 3 days before and (B) 5 weeks after closure of a patent ductus in a woman aged 66, showing a considerable reduction in heart size together with shrinkage of the main pulmonary artery and abolition of pulmonary plethora. The aortic knuckle is enlarged.

(A) (B)

FIG. 8.—6 ft. postero-anterior chest radiographs (A) before and (B) after closure of a patent ductus in a woman aged 49, showing a considerable reduction in the size of the heart and main pulmonary artery with abolition of pulmonary plethora. The aortic knuckle is enlarged.

monary arteriolar resistance was extreme (35 units) in the only case in which it was calculated.

Treatment and Progress

This group was not treated surgically because of the high mortality. Two of them are unchanged after a period of eighteen months and one has died. The patient who died developed sudden congestive cardiac failure. At post-mortem the duct was found to be very large (4 cm. diameter) as expected.

Discussion

The problems presented by patients with a left-to-right as opposed to a right-to-left shunt differ so markedly that we shall continue to consider the two groups separately.

A—Patent Ductus Arteriosus with a Left-to-Right Shunt

This is the common hæmodynamic state, being present in 40 out of 43 cases (93 per cent.), and there is seldom any difficulty in diagnosis in adults, as in children. The classical continuous murmur is present in at least 95 per cent. of cases, and when this is accompanied by a low diastolic blood pressure, cardiographic evidence of left ventricular hypertrophy, and a chest radiograph with pulmonary plethora and a dilated main pulmonary artery, the diagnosis is almost certain.

It is interesting that some patients do not develop symptoms until late in life (over the age of 60) and then may deteriorate quite rapidly. This could be due to the onset of ischæmic heart disease which becomes increasingly common with advancing years. The presence of a left-to-right shunt through a ductus raises the output of the left ventricle, and consequently increases the work required of the myocardium. If to this is added the additional disadvantage of myocardial ischæmia, it is easy to see how a rapid deterioration could occur, and how this could be relieved, at least partially, by closure of the duct. This could be one explanation of the sequence of events in patient 1 who was symptomless until after the age of 60. She then developed dyspnœa which progressed to congestive cardiac failure in the following five years. This was not due to pulmonary hypertension as the pulmonary arterial pressure was only 38/28. Closure produced a marked improvement, although there was still some disability in the form of exertional dyspnœa. In younger patients symptoms are unlikely to be due to ischæmic heart disease, and are probably completely explained on the basis of a left-to-right shunt throwing an additional burden on the left ventricle.

That the work performed by the myocardium may exceed the oxygen supplied to the muscle is shown by the strongly positive effort test in 1 patient and also by the occurrence of angina pectoris before, but not after, operation in 3 other patients.

The female : male ratio is between 2 and 3 : 1, and is approximately the

same in children as in adults, though women seem to predominate even more in the older age groups. The 4 patients so far on record over the age of 70 are all women, and in our series there were 5 women but no men over the age of 50, of whom 3 are now over 60. This could be explained on the grounds that men are more likely to develop coronary arterial disease which could make the prognosis worse in them than in women.

The pulmonary vascular resistance in these patients may remain normal for many years despite a greatly increased pulmonary blood flow, for an increased pulmonary flow does not necessarily cause obliterative pulmonary vascular disease (Wood, 1958). In patients with a patent ductus and a right-to-left shunt (Eisenmenger syndrome) the pulmonary vascular resistance is elevated from birth in 80 per cent. of the cases (Wood, 1958).

The real problem presented by this group is whether the duct should be closed and, if so, at what age. Clearly when there is considerable disability together with evidence of a large shunt, such as a low diastolic pressure, a mitral diastolic murmur, cardiac enlargement, pulmonary plethora, and left ventricular hypertrophy, there is no doubt that surgery is required. However, in the patient with no symptoms, and with signs of a small or moderate shunt, particularly with older age groups, the decision rests on an assessment of the prognosis with and without closure.

An accurate assessment of the prognosis without operation is difficult. Post-mortem series present a gloomy prospect with the average age at the time of death varying from 24 (Abbott, 1937) to 37 years (Keys and Shapiro, 1943). Bullock (1939) surveyed 80 cases and concluded that by the age of 14, 14 per cent. were dead, by the age of 30, 40 per cent., and by the age of 40, 71 per cent. were dead. Only 2 cases had survived to 66 years. Keys and Shapiro (1943) calculated that patients over the age of 17 with patent ductus have only half the life expectancy of normal people. However, as Brown (1950) has pointed out, autopsy figures represent a selected group and take little account of the living. Also, the prognosis has altered recently because the two major causes of death were bacterial endocarditis and congestive failure. While the latter is still as serious, the former is not, as the mortality from bacterial endocarditis has been greatly reduced by the introduction of antibiotics. Encouraging follow-up series have been published by Wilson and Lubschez (1942), who observed 38 cases for twenty years, but most of the patients were young adults even at the end of the follow-up period. Another factor to be considered is spontaneous closure of the duct as mentioned by Campbell (1955) and Cosh (1957). Only 4 of our cases were not treated surgically, and we have not therefore observed this. However, from the rarity of patent ductus arteriosus in elderly people, it is probable that the condition is associated with a reduced expectation of life.

The prognosis with operation is easier to assess because closure of the duct restores the hæmodynamics to normal and abolishes the risk of bacterial endocarditis.

The mortality varies. Gross (1952) in a series of 525 patients concluded that in the absence of congestive cardiac failure it was 0·5 per cent., but it may be as

high as 2 per cent. in some cases (Crafoord, 1948). However, it seems likely that in symptomless patients it is as low as 0·5 per cent. or lower.

The two main post-operative complications, apart from the transient ones which may complicate any thoracotomy, are re-canalisation and damage to the left recurrent laryngeal nerve. Re-canalisation is rare and often occurs, as in one of our cases, when the duct is closed while it is infected. This was performed before the advent of chemotherapy to cure the condition (Keele and Tubbs, 1940; Touroff and Vessel, 1940; Tubbs, 1944), but should seldom be necessary now. Damage to the recurrent laryngeal nerve, which is also rare, may be transient or permanent.

The beneficial results of operation are observed at all ages, and may be assessed by symptomatic improvement, rise of diastolic blood pressure, abolition of pulmonary plethora and reduction in the size of the heart and main pulmonary artery. In all our cases the diastolic blood pressure rose and in the majority the heart was reduced in size. The continuous murmur and, where present, the mitral diastolic murmur were abolished, but 13 patients were left with a systolic pulmonary ejection murmur, due probably to some residual dilatation of the main pulmonary artery.

Thus against the almost certain development of disability in later life, together with a reduced life span, must be considered the advantages of a safe and completely curative operation with a low mortality. For these reasons, we recommend that all patients found to have a patent ductus arteriosus and an appreciable left-to-right shunt should receive surgical treatment, regardless of age and lack of symptoms.

B—Patent Ductus Arteriosus with a Right-to-Left Shunt due to Pulmonary Hypertension (Eisenmenger Reaction)

There were only 3 patients in this group (7 per cent. of the total) but they illustrate the features well.

Surgical treatment has not been attempted in our patients, owing to the high mortality. If an associated left-to-right shunt is present, then ligation of the duct is justifiable if the pulmonary artery pressure falls on compression of the duct at thoracotomy. We believe, however, that there is usually little place for surgery in these patients.

Summary

Forty-three patients with patent ductus arteriosus occurring in adult life are presented. The ages varied from 21 to 66 years.

The patients fall into two distinct groups sharing only enlargement of the main pulmonary artery on the chest radiograph (a finding present in all of our cases) and differing in most other respects.

Group A. Patent ductus arteriosus with a left-to-right shunt. There were 40 cases in this group, representing 93 per cent. of the total. The clinical assessment before operation is discussed with particular reference to the symptoms of

dyspnœa and angina. Patients with a patent ductus may remain symptomless until middle life, but may then deteriorate rapidly.

Angina of effort, not previously described, may occur and is thought to be due to increased left ventricular work rather than to coronary artery disease, although the latter may explain the marked preponderance of women over men in later life.

The classical murmur was present in all but 1 of our patients, and in 9 patients there was a mitral diastolic murmur representing a large shunt.

The pulmonary vascular resistance may remain normal for many years, despite a greatly increased pulmonary blood flow.

The results of operation are presented, with particular reference to the low operative mortality, the dramatic improvement in symptoms, the rise of diastolic blood pressure and reduction in heart size.

Arguments are advanced for closing the patent ductus with an appreciable left-to-right shunt, regardless of age and lack of symptoms.

Special mention is made of 2 patients, one of whom had surgical treatment at the age of 66. To our knowledge she is the oldest patient to have had the operation.

Group B. Patent ductus arteriosus with a right-to-left shunt due to pulmonary hypertension (Eisenmenger reaction). There were 3 patients in this group (7 per cent.) aged 30, 42 and 48 years respectively, and operation was not advised.

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REFERENCES

Abbott, M. E. (1937): "Nelson's Loose-leaf Medicine." Nelson, N.Y., **4**, 266.
Bain, C. W. C. (1957): *Brit. Heart J.*, **19**, 574.
Benn, J. (1947): *Ibid.*, **9**, 283.
Bothwell, T. H., Van Lingen, B., Whidborne, J., Kaye, J., MacGregor, M., and Elliott, G. A. (1952): *Amer. Heart J.*, **44**, 360.
Brown, J. W. (1950): "Congenital Heart Disease," 2nd Ed. London: Staples Press.
Bullock, L. T., Jones, J. C., and Dolley, F. S. (1939): *J. Pediat.*, **15**, 786.
Campbell, M. (1955): *Brit. Heart J.*, **17**, 511.
Campbell, M., and Hudson, R. (1951): *Guy's Hosp. Rep.*, **100**, 26.
Cosh, J. A. (1953): *Brit. Heart J.*, **15**, 423.
(1957): *Ibid.*, **19**, 13.
Crafoord, C. (1948): *Ibid.*, **10**, 74.
Dammann, J. F., Jnr., and Sell, C. G. R. (1952): *Circulation (N.Y.)*, **6**, 110.
Ellis, F. H., Jnr., Kirklin, J. W., Callahan, J. A., and Wood, E. H. (1956): *J. thorac. Surg.*, **31**, 268.
Fishman, L., and Silverthorne, M. C. (1951): *Amer. Heart J.*, **41**, 762.
Fleming, P., and Gibson, R. (1957): *Thorax*, **12**, 37.
Gibson, G. A. (1900): *Edinb. med. J.*, **8**, 1.
Gross, R. E. (1943): *N.Y. St. J. Med.*, **43**, 1856.
(1952): *Amer. J. Med.*, **12**, 472.
Gross, R. E., and Hubbard, J. P. (1939): *J. Amer. med. Ass.*, **112**, 729.
Harris, P. (1955): *Brit. Heart J.*, **17**, 85.
Holman, E., Gerbode, F., and Purdy, A. (1953): *J. thorac. Surg.*, **25**, 111.
Hultgren, H., Selzer, A., Purdy, A., Holman, E., and Gerbode, F. (1953): *Circulation (N.Y.)*, **8**, 15.

JOHNSON, R. E., WERMER, P., KRUSCHNER, M., and COURNAND, A. (1950): *Circulation (N.Y.)*, **1**, 1293.
KEELE, K. D., and TUBBS, O. S. (1940): *St. Bart's Hosp. J.*, **1**, 175.
KEYS, A., and SHAPIRO, M. J. (1943): *Amer. Heart J.*, **25**, 158.
KUHN, L. A. (1958): *J. Mt Sinai Hosp.*, **25**, No. 2, 103.
SMITH, G. (1954): *Brit. Heart J.*, **16**, 23.
STORSTEIN, O., HUMERFELT, S., MULLER, O., and RASMUSSEN, H. (1952): *Ibid.*, **14**, 276.
TOUROFF, A. S. W., and VESSELL, H. (1940): *J. Amer. med. Ass.*, **115**, 1270.
TUBBS, O. S. (1944): *Brit. J. Surg.*, **32**, 1.
WHITTAKER, W., HEATH, D., and BROWN, J. W. (1955): *Brit. Heart J.*, **17**, 121.
WILSON, M. G., and LUBSCHEZ, R. (1942): *J. Pediat.*, **21**, 23.
WOOD, P. (1956): "Diseases of the Heart and Circulation." 2nd Ed. London: Eyre and Spottiswoode.
(1958): *Brit. med. J.*, **2**, 701, 755.

Brit. J. Dis. Chest (1959) **53**, 278.

BRONCHIAL ABNORMALITIES AFTER PRIMARY TUBERCULOSIS

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After Ghon's classical paper in 1912 on the pathology of the primary tuberculous complex in children, the clinical picture accompanying primary tuberculosis was not appreciated until Eliasberg and Neuland's description in 1920. These authors wrote of children showing massive homogeneous pulmonary shadowing, usually of lobar distribution, which generally persisted for months. This they contrasted with the mild constitutional symptoms—such as dry cough and low-grade fever, with complete absence of dyspnœa. The tuberculin test was invariably strongly positive. When clearing finally took place it did so from the periphery, sometimes leaving in its wake what appeared to be mediastinal glands. The authors stressed (1921) that resolution was always satisfactory without residual fibrosis, collapse or bronchiectasis, and considered the clinical and radiological picture a non-specific reaction to the primary tuberculous infection of the lungs. They gave the condition the name "epituberculosis."

This view of the benign prognosis and absence of sequelæ to the primary tuberculous infection prevailed until the mid-thirties, when Salomonsen and Traetteberg (1935) pointed out residual X-ray shadows, such as fibrous patches, persistent collapse and possible bronchiectasis in children with previous epituberculosis. Brock, Cann and Dickinson (1937) showed eight cases of primary tuberculosis with bronchial obstruction and suggested that bronchiectasis and bronchial stricture might follow.

Kent (1942) was the first systematically to follow with bronchogram certain children who had previously shown massive pulmonary shadowing with their primary complex. He found bronchiectasis in 7 out of 10 children so examined. Thereafter several different authors found bronchial abnormalities following primary tuberculosis in 14 to 86 per cent. of their studied cases (see Table 1). This represented a considerable variation in opinion, and on the whole the greater the number followed up with bronchography, the larger was the percentage of abnormality found.

In order to gain more accurate information on the incidence of these abnormalities and the role which they might play in the production of symptoms the present work was undertaken and was planned from two aspects: *Part* 1: A follow-up with bronchographic studies of an unselected series of children who had previously been admitted to hospital with a primary tuberculous complex showing radiological evidence of collapse. *Part* 2: A retrospective study of the records of bronchiectatic patients of all age groups, admitted to hospital during a ten-year period for investigation and treatment of this complaint.

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TABLE I.—COMPARISON OF RESULTS BY PREVIOUS AUTHORS AND PRESENT SERIES

	Total No. of cases	*No. with broncho-gram*	*Bronchiectasis*	*Non-filling*	*Stricture*	*Lobe or side involved most often*	*Bronchoscopic bronchial involvement*	*Percentage bronchial abnormality*
Kent (1942)	10	10	7	—	—	?	—	70
Meneghello and Smith (1943)	7	?	1	—	—	—	—	14
Richards (1944)	64	?	10	—	—	—	—	15
Jones, Peck and Willis (1946)	85	37	24	3	Rare	Sides equally involved	13	73
Roberts and Blair (1950) ..	77	37	34	—	—	Rt. upper. In addition 12 showed bronchiectasis on plain radiography	—	62
McPherson and Lutwyche (1950)	39	13	3	—	—	—	?	23
Hutchison (1951)	34	34	18	4	—	—	—	65
Jeune *et al.* (1951)	47	42	30	—	5	Right upper	26	71
Hardy *et al.* (1952) ..	35	28	20	—	—	Equally involved	—	70
Veeneklaas (1952)	51	51	15 plus 5 deformed	—	12	Right upper	Frequent	40
Williams and Anderson (1953)	40	37	32	—	10	Right upper	32	86
Adler and Richards (1953)	83	10	7	—	—	Rt. lung in 72%	71	70
Thomas *et al.* (1954) ..	44	?	7	—	—	—	—	16
Hughes and Ray (1958) ..	99	65	16	13	2	—	25 out of 56	45
Present series	116	71	29 plus 10 with deformed bronchi	2	3	Right upper	21 out of 25	58

Pathological Considerations

In this study the X-ray opacity produced by primary tuberculosis will be described as " collapse," although it is fully realised that factors other than simple collapse may produce the final picture. There is, in fact, considerable controversy as to the pathology underlying the radiological shadows seen, but three types of lesions have been described either singly or in conjunction (Goldberg and Gasul, 1930; Cameron and Navasquez, 1936; MacGregor and Alexander, 1937; Fish and Pagel, 1938):

1. Proliferative infiltration and granulomata. This was a direct extension of the cellular reaction always occurring around the primary focus, and might involve large areas of lung tissue. It may produce fibrosis with healing.

2. A specific tuberculous allergic reaction which was thought probably due to the products of the tubercle bacillus. This was supported by the finding that in children recently recovered from primary tuberculosis the injection of old tuberculin produced a recurrence of the massive pulmonary shadowing (Langer, 1922; Kleinschmidt, 1926). Extensive consolidation without caseation was found, the alveoli being filled with mononuclear cells. There was a tendency to organisation and fibroblastic proliferation.

3. Collapse due to obstruction of a bronchus by an enlarged gland involved in the primary complex pressing from outside or actually perforating the bronchial wall and filling the lumen with granulation tissue on caseous material (Wallgren, 1926; Prosoroff, 1929; Pinchin and Morlock, 1933, and de Bruin, 1936). De Bruin further pointed out that the slow bronchial occlusion with incomplete absorption of air, accompanied by retention of secretions, produced an atypical radiological picture of collapse—that of a " drowned lobe."

All authors remarked on the scarcity or complete absence of acid-fast bacilli.

Material and Methods

Part 1. The material was drawn from 176 children admitted to hospital for the treatment of primary tuberculosis between 1948 and 1954. Of these 116 showed evidence of pulmonary collapse and were therefore considered suitable for further investigation by bronchography. This investigation was carried out in 78 cases, the remaining 38 either refusing or being unavailable for this examination. Seven children who did have bronchograms were excluded as it was evident that their primary infection had occurred some time before coming under observation and records of the severity and duration of their pulmonary collapse were insufficient. This left 71 cases for final discussion.

Table II shows their age and sex incidence at the time of the primary infection.

All these children are still seen regularly in the out-patient department. Forty-six of them (64·8 per cent.) have been followed for more than five years.

Bronchography was not performed until it was felt that the primary tuberculous infection had healed, usually between two and four years after discharge from hospital. Two bronchograms were done within a year of discharge from hospital, both for non-medical reasons.

TABLE II.—AGE AND SEX INCIDENCE AT TIME OF PRIMARY INFECTION (CHILDREN WITH PULMONARY COLLAPSE)

Age in years	*Total number*	*Boys*	*Girls*
0-2	7	5	2
2-5	24	11	13
5-10	36	22	14
10-15	3	2	1
15+	1	1	—
Total ..	71	41	30

Part 2. The records were studied of 562 patients admitted to the thoracic unit in the ten-year period 1946-55 and diagnosed as suffering from bronchiectasis.

The time of onset of symptoms and whether it was directly related to any illness was noted; also if there had been previous chest illness, especially primary tuberculosis; in children the tuberculin reaction was recorded. In 535 cases (95 per cent.) the diagnosis of bronchiectasis was confirmed by bronchogram. Of the remainder, 13 cases (2·3 per cent.) had tomograms and 14 others (2·5 per cent.) had obvious cystic changes. Pulmonary calcification was noted, if in relation to the bronchiectatic area. Where bronchoscopy had been performed special note was taken of bronchial stricture. In the 370 cases where resection was performed the records were studied for remarks on calcified glands, or glands densely adherent to the bronchus of the affected segment.

The histological findings on the resected material in 151 cases were examined for evidence of old primary tuberculosis.

From all these data a conclusion was drawn as to the probability of primary tuberculosis being the cause of bronchiectasis.

The ages of the patients in this group ranged from 13 months to 71 years, but in the majority of cases they were young adults and children, 280 (49·2 per cent.) falling between the ages of 10 and 20 years. There was no obvious difference in sex distribution. No patient was included in this group who was known to be suffering from adult tuberculosis, and no case included in Part 1 was again included in Part 2.

Results

PART 1. BRONCHOGRAPHIC FINDINGS AFTER PRIMARY TUBERCULOSIS

Of the 71 children in this series 29 (40·8 per cent.) showed frank bronchiectasis. Three of the children had a definite and one a probable stricture. Ten cases (14 per cent.) showed irregularity of the bronchi, not amounting to bronchiectasis. Five (7 per cent.) showed crowding of the bronchi, which were however of normal shape and calibre. In 2 (2·8 per cent.) the segment previously affected by the primary complex failed to fill, suggesting a bronchial stricture.

In one case a diverticulum of a main bronchus was found although the peripheral bronchi were normal. Twenty-four (33·8 per cent.) were completely normal.

Thus 47 children (66·2 per cent.) showed some abnormality of the bronchial tree following primary tuberculosis. The pattern of distribution of bronchial abnormalities followed closely on that of the previous collapse during the acute stage. The right lung, in particular the right upper and middle lobes (either singly or together), bore the brunt of the attack, being involved in two-thirds of the cases. Thus the right upper lobe was affected by collapse in 30·9 per cent. of cases and subsequently by bronchiectasis in 32 per cent. (equally 32 per cent. of total bronchial abnormalities). The figures for the right middle lobe were: collapse 33 per cent., bronchiectasis 32 per cent., and total bronchial abnormalities 37 per cent. In only one was a segment of bronchiectasis found in an area not previously collapsed during the active stage.

TABLE III.—RELATION BETWEEN BRONCHOSCOPIC FINDINGS AND FINAL RESULT

Bronchoscopic finding	*Bronchiectasis*	*Irregularity of bronchi*	*Crowding of bronchi*	*Normal*	*Total*
Normal	2	1	—	1	4
Œdema	2	—	—	—	2
Endobronchial granulations ..	5	1	2	3	11
Extrinsic pressure ..	5	1	—	2	8
Number bronchoscoped	14	3	2	6	25

In order to gain more information as to the factors which might predispose to the development of bronchial abnormalities the above findings were further studied in relation to the age of the child, the duration of collapse and bronchoscopic findings.

Age. Of the 7 children under 2 years, 6 (86 per cent.) developed bronchial abnormalities of some degree. Four of these (57·1 per cent.) showed frank bronchiectasis. In the 2-5 year and 5-10 year age groups the figures for bronchiectasis were 33·3 and 41·6 per cent. respectively, total bronchial abnormalities developing in 62·5 and 66·6 per cent. respectively. There were only 3 children in the 10-15 year group; 1 of these developed bronchiectasis.

Although these figures deal with only small numbers, they do suggest that infants under 2 years of age are particularly liable to develop bronchial abnormalities.

Duration of Collapse. This was difficult to assess with accuracy, as most children were admitted with the affected part already collapsed, and several never showed complete re-expansion. Noting the time of dense radiological opacity during the " acute " stage until re-aeration seemed to start, it was found that the shortest period of collapse was 3 months, and the longest 32 months. In the bronchiectatic group the average time of collapse was 10·9

TABLE IV.—CORRELATION OF THE PRINCIPAL FINDINGS IN CHILDREN WITH PRIMARY TUBERCULOUS COMPLEX

	No. of cases	*Lobes most often affected*	*Plain X-ray appearance*	*Average duration of collapse (months)*	*Bronchoscopic findings*	*Liability of age-group to develop bronchiectasis*
Bronchiectasis ..	29	Right upper and middle	86% abnormal	10·9	85% positive (14 cases)	Infants most liable to develop bronchiectasis.
Bronchial irregularity	10	Right upper and middle	56% abnormal	6·8	66% positive (3 cases)	No particular age distribution.
Collapse only	5	Right middle	40% abnormal	6·8	100% positive (2 cases)	No particular age distribution.
Stricture	4	Right upper	83% abnormal	12·5	100% positive (1 case)	No particular age distribution.
Normal	24	Left upper	41·4% abnormal	7·0	83% positive (6 cases)	Infants most likely to be abnormal.

months. In the group where there was only irregularity or crowding of the bronchi, the average duration of collapse was 6·8 months; this figure is comparable to the " normal " group, in which collapse averaged 7 months. These figures would suggest, therefore, that longer duration of collapse increases the liability to develop bronchiectasis.

Bronchoscopic Findings. Twenty-five children were examined by bronchoscopy, many on more than one occasion. Of these 11 showed endobronchial granulations, 8 extrinsic compression of a bronchus, 2 mucosal œdema and 4 no abnormality.

Table III shows the result of bronchoscopic findings and the outcome of the primary complex. Again the numbers are small, but suggest that bronchial obstruction either by granulations or extrinsic pressure predisposed heavily to permanent bronchial abnormality.

Symptoms. Of the 47 children with bronchial abnormalities 14 (29·7 per cent.) have developed symptoms while under observation. Eleven of these were bronchiectatic, 2 showed crowding of the bronchi of the affected segment, and 1 had crowding and slight irregularity of the bronchi. The most common symptom was dry cough (5 cases) or cough and sputum (3 cases), while one or more attacks of bronchitis were experienced by a further 3. Non-specific infection (pneumonia or transient consolidation) in the previously affected segment occurred in 2, and 1 had recurrent upper respiratory tract infection.

The principal findings of Part 1 are summarized in Table IV.

Part 2. Bronchiectasis from All Causes

Of the 562 bronchiectatics 30 (5·9 per cent.) were thought on the evidence available to have developed bronchiectasis as a result of primary tuberculosis. In 15 there was definite histological evidence of this from resected lobes and glands. In the remaining 15 there was heavy calcification in relation to the bronchiectatic segment; 2 of these also had bronchial strictures. Only 1 gave a history of having had a primary complex.

To give some measure of perspective the presenting symptoms and suspected causal factors in these 562 bronchiectatics are listed in Table V and the number thought to have been due to a primary tuberculous complex is given in each group. Table I compares the findings in Part 1 of this series with those of other authors.

Discussion

The finding that bronchial abnormalities developed in 66·2 per cent. of children with previous primary tuberculous complex showing pulmonary collapse agrees with the majority of publications which put the incidence of this complication at between 49 and 80 per cent. In the present series the incidence of frank bronchiectasis is somewhat lower—40·8 per cent. A number of authors would call bronchiectasis the abnormality which we have considered separately under the heading of " bronchial irregularity " without actual dilatation. In fact, of all the authors studied, only Veeneklaas (1952) and Hutchison (1951) give this special mention.

TABLE V.—PRESENTING HISTORY OF BRONCHIECTATICS AND NUMBER THOUGHT DUE TO PRIMARY TUBERCULOSIS

Presenting symptoms and/or history	*Total number*	*Primary tuberculous complex*		
		Total	*Proven*	*Probable*
Cough following pneumonia	204	7	4	3
Cough dating back to childhood without definite history of onset	135	7	4	3
Cough following whooping cough	52	—	—	—
Cough of insidious onset but not dating back to childhood (duration of from 3 months to 10 years)	47	9	5	4
Cough following measles	28	—	—	—
Hæmoptysis	22	3	1	2
Asthma	16	1	—	1
Chronic sinus infection	15	—	—	—
Cough following removal of tonsils and adenoids	6	—	—	—
Cough following other general anæsthetic	6	—	—	—
Lung abscess	4	—	—	—
Other infectious fevers	4	—	—	—
Inhalation of foreign body	3	—	—	—
Miscellaneous	9	2	—	2
No history available	10	—	—	—
Primary tuberculosis complex	1	1	1	—
Total	562	30	15	15

Some of the published figures cannot be accepted unconditionally as most authors exercised some selection of cases for bronchography. The 71 children who had bronchograms in the present series were not specially selected.

A further source of error in published works is the diagnosis of bronchiectasis on plain X-ray.

An erroneous picture may also be gained by doing a bronchogram too soon after the occurrence of the primary complex. Hutchison (1949) has shown that bronchiectasis present in the acute stage of the primary complex may revert to normal up to 1 year after resolution. In the present series only two bronchograms were done within 1 year of discharge from hospital.

DISTRIBUTION AND TYPE OF BRONCHIECTASIS

The right lung is involved by the primary tuberculous complex more frequently than the left (Ghon, 1912; MacGregor and Alexander, 1937; Richards, 1944, Graham and Hutchinson, 1947; Carlens and Hellström, 1953), and most authors find the right upper and right middle lobes particularly liable to collapse and subsequent bronchiectasis (Richards, 1944; Graham and Hutchison, 1947; Roberts and Blair, 1950). The present series strongly supports this view. Thus bronchiectasis following primary tuberculosis differs from that due to other causes in which the left side, especially the left lower lobe is mainly involved. This lobe was involved in 65·1 per cent. of all bronchiectatics, but only in 20 per cent. of those in whom bronchiectasis was thought

to be of primary tuberculous ætiology in Part 2 of this series. In these latter the right upper and middle lobe were affected in 56 per cent. The anatomical arrangement of glands grouped around the right middle lobe bronchus has been thought to be the cause of the frequent collapse of this lobe (Brock, 1950). The glands surrounding this bronchus drain also the upper and lower lobes on the right (Graham *et al.*, 1948) and may therefore by pressure cause middle lobe collapse even when the primary focus is not situated in this lobe (Jones *et al.*, 1946). Our own figures and those of Roberts and Blair (1950) and Williams and Anderson (1953) do not support the theory that the right middle lobe is more vulnerable than the right upper lobe, and bronchial stenosis was not once found in the middle lobe bronchus, but occurred in the right upper lobe bronchus in all 4 cases (see Fig. 1).*

The type of bronchiectasis following primary tuberculosis is generally accepted to be cylindrical, only Adler and Richards (1953) and Hardy *et al.* (1952) describing it as saccular. All the cases in the present series were of the cylindrical type.

The finding of bronchial irregularities apart from frank bronchiectasis might be thought to be a transitional stage to recovery, but it was often found as long as 4 years after the original primary infection, and must therefore be considered permanent.

Persistent collapse of lobes without bronchiectasis was found in 5 per cent. of the present series; this corresponds roughly with the findings of Hutchison (1951), McPherson and Lutwyche (1950) and Roberts and Blair (1950). It is not certain whether these will eventually re-expand or, on the other hand, become bronchiectatic.

No reference has been found in the literature to a diverticulum of a major bronchus caused through involvement by a tuberculous gland. One case was noted in this series (case 38, W.M.) and illustrated in Fig. 2. No bronchiectasis was present. Presumably the diverticulum marks the point where a tuberculous gland eroded into the bronchus and weakened its wall.

Factors in the Development of Bronchiectasis

Both the duration of the collapse and the age of the child appear to have a very definite bearing on the development of bronchiectasis. Thus Hardy and co-workers (1952) found that more than half of the children who developed bronchiectasis were under 2 years of age. Adler and Richards (1953) stated that children under 6 years of age were three times more likely to develop pulmonary collapse from bronchial compression than those older; this view was also upheld by Thomas *et al.* (1954). Wallgren (1935) further suggested that healing was slower in the smaller children. In the present series there is a definite impression that infants develop bronchiectasis more easily, only 1 out of 7 escaping with a completely normal bronchial tree. It is probable that the narrow, easily compressed and obstructed bronchi are responsible. No difference has been found between the very young and older children in the time it took for the primary focus to heal.

* The figure numbers in the text refer to Plate XLIV.

The average time taken for the characteristic pulmonary shadow of primary tuberculosis to resolve is 6-18 months (Eliasberg and Neuland, 1920; Adler and Richards, 1953) and the longer collapse is present the more likely is the child to develop bronchiectasis. The findings in this paper agree with this view. Half (55 per cent.) of the children who developed bronchial abnormalities showed pulmonary collapse for longer than 9 months, whereas in those who remained normal the majority (70 per cent.) had collapse for less than 9 months. There were, nevertheless, patients who developed bronchiectasis although they showed collapse for only 3-6 months, and similarly 2 children remained normal although collapse had been present for nearly 15 months.

Bronchoscopy

Bronchoscopic findings, especially those of bronchial compression and obstruction, are closely related to the final outcome. The bronchoscopic appearances may be narrowing of the lumen from the outside; œdema of the bronchial mucosa with the tuberculous gland " pointing " locally; and actual perforation of the bronchial wall with tuberculous granulations or caseous material obstructing the lumen. Compression may be seen quite early (in the first 3 months), but actual perforation is uncommon before 5-6 months from the beginning of the primary complex. Adler and Richards (1953) found that in 33 of their 35 cases showing bronchoscopic changes permanent collapse resulted; 10 of these had bronchograms and 7 were found to be bronchiectatic. Jeune *et al.* (1951) found that 77 per cent. of 26 cases with bronchial involvement developed bronchiectasis, whereas of the 21 without bronchial involvement 47 per cent. became bronchiectatic. In the present series only 25 of the 71 children were bronchoscoped and the figures are, therefore, not conclusive. But the finding of bronchial involvement in 5 children out of 6 subsequently normal as compared to bronchial involvement in 12 out of 14 who developed bronchiectasis (see Table II) may indicate that the ability to remove bronchial granulations through the bronchoscope diminishes the liability to develop bronchiectasis.

Assessment of Risk

The childhood incidence of pulmonary collapse in primary tuberculosis is given by Thompson (1952) as 4·2 per cent. and by McPherson (1939) as 4·7 per cent. Other assessments range as high as 17 per cent. (Thomas *et al.*, 1954). If, therefore, about 50 per cent. of these children develop bronchiectasis, an estimated 2·1 per cent. at the very least are at risk. This figure compares with that for the incidence of bronchiectasis following whooping cough, for which 2·6 per cent. is given by Lees (1950) or 1·9 per cent. by James *et al.* (1956).

Thus primary tuberculosis is an important factor in the ætiology of bronchiectasis. The predilection of the disease for the upper lobes enables by self-drainage two-thirds of the patients to remain free from symptoms for over 5 years, but these may supervene in adult life, sometimes with dramatic suddenness (Brock, 1950). We have shown in Part 2 that in 5·9 per cent. of

562 bronchiectatics the cause was primary tuberculosis. This figure compares well with the 6 per cent. given by Oswald (1956), though somewhat higher than the 2·5 per cent. quoted by Field (1949). Therefore every effort should be made to prevent the development of bronchiectasis in cases with primary tuberculosis.

Prophylaxis

Chemotherapy with streptomycin, para-amino-salicylic acid or isoniazid has little effect on the actual course of the primary complex and its glandular component, and it does not prevent pulmonary collapse from occurring (Williams and Anderson, 1953).

As bronchial obstruction is the most potent factor in the development of bronchiectasis, bronchoscopy would seem to be indicated in all cases of primary tuberculosis with collapse persisting for more than 3 months, and removal of endobronchial granulations at intervals is advocated where possible for as long as collapse remains. In only a proportion of cases is bronchial obstruction visible through the bronchoscope and, even in these, re-aeration does not inevitably follow clearing of endobronchial granulations.

In the experience gained from the present series it can be said that, however well a bronchus seems to have been cleared by morcellement and suction, granulations almost invariably recur and require repeated bronchoscopic removal. The smaller the child the more difficult are these manœuvres, so that, with the recognised additional risk of severe laryngeal œdema, very few bronchoscopies have been performed on children under 3—those very cases in which clearing of the bronchus might be most valuable in preventing the development of bronchiectasis.

Because of the uncertainty of obtaining re-aeration of the collapsed portion of lung, Thomas (1952) and Giraud and Metras (1953) have advocated thoracotomy in these cases of persistent collapse; the latter authors claimed that re-aeration followed in every case; Thomas stated that removal of the diseased lobe may be necessary, while Seal and he (1956) again upheld this view with the finding that the resected specimens of lung showed a tuberculous pneumonia either caseous or non-caseous, and that visible atelectasis was never encountered. Chesterman (1957) goes so far as to suggest that gland pressure giving rise to an area of pulmonary collapse lasting for more than one month should be treated surgically by removal of the gland or incision and evacuation of its contents.

Major surgery may have a rare place in the treatment of this condition when there is severe stridor with cyanotic attacks from mediastinal gland pressure, but a more cautious attitude might well be taken when surgery is suggested in the active stage of the disease, for " gross distortion of the bronchial tree " or " lack of resolution or progression of the pulmonary shadow " (Thomas, 1952).

In this connection there are some points worthy of consideration:

1. The prognosis as regards life throughout the primary phase of tuberculous infection, however prolonged, is so good that any drastic action requires full justification. Although modern anti-tuberculous substances may have a disappointing effect on the primary complex itself, their control of the severe

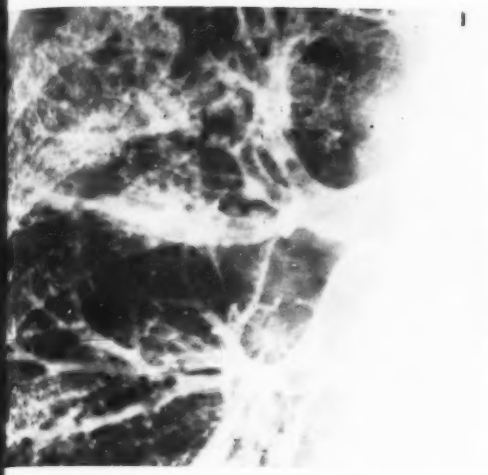

FIG. 1.—(Case 57.) Bronchogram—Stricture at origin of anterior segment, right upper lobe.

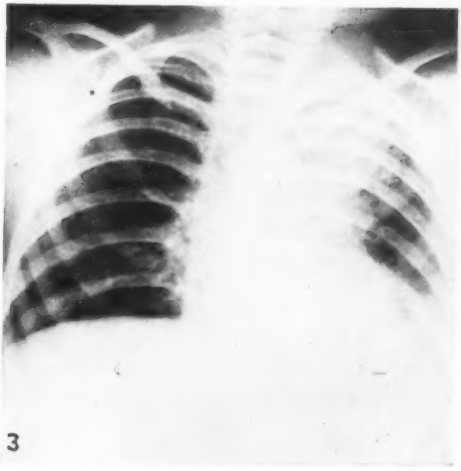

FIG. 3.—(Case 9.) Collapse of left upper lobe with basal segmental collapse in left lower lobe.

FIG. 2.—(Case 38.) Bronchogram—Bronchial diverticulum.

FIG. 3A.—(Case 9.) Bronchogram—residual bronchiectasis confined to apical and posterior segments of left upper lobe.

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hæmatogenous complications has been dramatic. The mortality of any operation, during the active stage, must be set against this fact.

2. While justification might be given to the idea of removing any caseous pulmonary focus of doubtful activity such as might cause later endogenous spread of infection, Heaf (1956) hopes that it will in future be possible to avoid the caseous residue by combining adequate drug treatment with artificially induced hyposensitivity of the patient.

3. It cannot be foretold which of the children with primary tuberculosis and " collapse " are going to develop bronchiectasis, and, if so, what its extent will be. Early resection might remove far more lung segments than would ultimately become bronchiectatic, and it has been shown that bronchiectasis may not remain even if " collapse " has lasted for over 1 year (see Figs. III and IIIA). Resection in the active tuberculous stage cannot therefore be justified by the later findings of bronchial abnormalities, especially as this type of bronchiectatic may remain so free from symptoms. Operations for the removal or evacuation of affected glands may be more easily defensible, but even so should be confined to selected cases.

With Bentley (1956) and Cameron *et al.* (1957), therefore, the present authors feel that more evidence is needed to justify wholesale thoracic operations upon children with primary tuberculosis during the active phase and in the meantime the pursuit of bronchoscopic treatment where possible is rational, although at times disappointing. Whether surgery is necessary later in life for bronchiectasis must be assessed on the criteria to be applied to any bronchiectatic subject who presents for consideration of resection.

Pathogenesis of Bronchiectasis

The difficulty in assessing the exact pathological anatomy of a dense pulmonary shadow complicating primary tuberculosis has already been admitted; there is some doubt therefore whether correct deductions can be made about the mechanism of bronchiectasis production in these cases. Presumably the factors are comparable with other forms of bronchiectasis, namely bronchial obstruction, either by extrinsic pressure of a tuberculous gland or by granulation tissue after erosion through the bronchus, and infection, which in these cases is tuberculous and possibly of the type described by MacGregor and Alexander (1937).

Various authors have put forward the theory that direct damage to the bronchus by tuberculous involvement occurs with distension of bronchi by caseous material (Jones *et al.*, 1946; Roberts and Blair, 1950), but in the present work it has been found that children who must have had extensive caseation, as shown by calcification throughout a lobe, but without bronchial obstruction, had not on recovery developed bronchiectasis. Thus it would seem that caseation alone without an obstructive factor will not produce bronchiectasis.

It is almost impossible to predict solely on radiological evidence whether bronchiectasis is likely to develop. A radiological shadow may mean a number of things, either collapse, consolidation, tuberculous pneumonia or caseation,

or two of these together. The main factors which influence prognosis are the age of the child, the duration of collapse and whether it is possible to aid the clearing of any bronchial obstruction sufficiently early.

Conclusions

1. Bronchiectasis develops in 40·8 per cent. of children after primary tuberculosis which gives rise to pulmonary collapse. A further 14 per cent. show bronchial irregularity. Stricture formation is rare.

2. At least 2·1 per cent. of children with a pulmonary primary tuberculous complex develop bronchiectasis, a percentage approximating to that after whooping cough.

3. The younger the child affected with pulmonary collapse and the longer the duration of such collapse, the more likely is bronchiectasis to develop.

4. The right upper and middle lobes are most frequently affected and the anatomical distribution of bronchiectasis after primary tuberculosis thus differs from that of bronchiectasis from other causes.

5. The majority of children developing bronchiectasis after primary tuberculosis are symptom free for several years, and many will not develop symptoms until adult life, if at all. This is thought to be due to the predilection of the primary complex for the upper lobes, so that bronchiectasis in this situation remains " dry " on account of self-drainage.

6. The factor responsible for the production of bronchiectasis is bronchial obstruction by a tuberculous gland, whether by extrinsic pressure or by erosion through the bronchial wall with the development of endobronchial granulations. Tuberculous infection of the bronchial tree probably also plays a part, but only in conjunction with the obstructive element.

7. At least 5·9 per cent. of all established bronchiectatics with symptoms are considered to have a primary tuberculous ætiology.

Summary

Part 1. A follow-up with bronchographic studies is made of 71 children with primary tuberculosis showing pulmonary collapse.

The incidence of bronchiectasis following this condition is determined and the special features of bronchiectasis and other bronchial abnormalities following primary tuberculosis are noted.

The possible factors leading to the development of bronchiectasis are investigated with special reference to the length of time of collapse, bronchoscopic appearances and age incidence.

Part 2. The case histories, radiological, pathological and operative findings of 562 patients diagnosed as suffering from bronchiectasis are briefly reviewed in retrospect.

The number thought due to various common diseases, such as pneumonia, infectious fevers, etc., is determined and those cases are noted in whom primary tuberculosis was thought to have caused bronchiectasis.

The results in the present series are discussed in relation to the findings by other authors.

A note is made of the number of children at risk and the probability of bronchiectasis developing, and its possible prevention is discussed.

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REFERENCES

ADLER, D., and RICHARDS, W. F. (1953): *Thorax*, **8**, 223.
BENTLEY, F. J. (1956): *Lancet*, **2**, 1160.
BROCK, R. C. (1950): *Thorax*, **5**, 5.
BROCK, R. C., CANN, R. J., and DICKINSON, J. R. (1937): *Guy's Hosp. Rep.*, **87**, 295.
DE BRUIN, M. (1936): *Arch. Dis. Childh.*, **11**, 65.
CAMERON, H. C., and DE NAVASQUEZ, S. (1936): *Guy's Hosp. Rep.*, **86**, 366.
CARLENS, E., and HELLSTRÖM, B. E. (1953): *Acta paediat. (Uppsala)*, **42**, 43.
CHESTERMAN, J. T. (1957): *Thorax*, **12**, 159.
ELIASBERG, H., and NEULAND, W. (1920): *J. Kinderheilk.*, **93**, 88.
(1921): *Ibid.*, **94**, 102.
FIELD, C. E. (1949): *Pediatrics*, **4**, 21.
FISH, R. H., and PAGEL, W. (1938): *J. Path. Bact.*, **47**, 593.
GHON, A. (1912): "Der Primäre Lungenherd bei der Tuberculose." Vienna: Urban and Schwartzenberg, 19.
GIRAUD, P., and METRAS, H. (1953): *Rev. Tuberc. (Paris)*, 5, Ser. 17. Nos. 4-5, 437.
GOLDBERG, B., and GASUL, B. (1930): *Amer. J. med. Sci.*, **180**, 824.
GRAHAM, E. A., BURFORD, T. H., and MAYER, J. H. (1948): *Postgrad. Med.*, **4**, 29.
GRAHAM, S., and HUTCHISON, J. H. (1947): *Arch. Dis. Childh.*, **22**, 162.
HARDY, J. B., PROCTOR, D. F., and TURNER, J. A. (1952): *J. Pediat.*, **41**, 740.
HEAF, F. (1956): *Lancet*, **2**, 1101.
HUGHES, E. W., and RAY, R. L. (1958): *Thorax*, **13**, 74.
HUTCHISON, J. H. (1951): *Tubercle*, **32**, 271.
JAMES, U., BRIMBLECOMBE, F. S. W., and WELLS, J. W. (1956): *Quart. J. Med.*, **25**, 121.
JEUNE, M., BERAUD, C., MOUNIER-KUHN, P., and NORMAND, J. (1951): *Sem. Hôp. Paris.*, **33**, 1442.
JONES, E. M., PECK, W. M., and WILLIS, H. S. (1946): *Amer. J. Dis. Child.*, **72**, 296.
KENT, E. M. (1942): *Amer. Rev. Tub.*, **46**, 392.
KLEINSCHMIDT, H. (1926): *Beitr. klin. Tuberk.*, **61**, 330.
LANGER, H. (1922/23): *Z. Kinderheilk.*, **34**, 60 (quoted by MacGregor and Alexander).
LEES, A. W. (1950): *Brit. med. J.*, **2**, 1138.
MACGREGOR, A. R., and ALEXANDER, W. A. (1937): *Edinb. med. J.*, **44**, 561.
MCPHERSON, A. M. C. (1939): *Brit. J. Tuberc.*, **33**, 79.
MCPHERSON, A. M., and LUTWYCHE, V. U. (1950): *Thorax*, **5**, 1.
MENEGHELLO, J., and SMITH, C. A. (1943): *J. Pediat.*, **22**, 265.
OSWALD, N. C. (1946): *Proc. roy. Soc. Med.*, **40**, 736.
PINCHIN, A. J. S., and MORLOCK, H. V. (1933): *Lancet*, **1**, 1114.
PROSOROFF, A. (1929): *Beitr. klin. Tuberk.*, **72**, 560.
RICHARDS, W. F. (1944): *Proc. roy. Soc. Med.*, **37**, 589.
ROBERTS, J. C., and BLAIR, L. G. (1950): *Lancet*, **1**, 386.
SALOMONSEN, L., and TRAETTEBERG, H. (1935): *Acta paediat. (Uppsala)*, **17**, (suppl.), 200.
SEAL, R. M. E., and THOMAS, D. M. E. (1956): *Lancet*, **2**, 995.
THOMAS, D. M. E. (1952): *Proc. roy. Soc. Med.*, **45**, 743.
THOMAS, J. H., MORGAN, D. B., and DAVIES, T. W. (1954): *Brit. med. J.*, **2**, 1325.
THOMPSON, B. C. (1952): *Proc. roy. Soc. Med.*, **45**, 741.
VEENEKLAAS, G. M. H. (1952): *Amer. J. Dis. Child.*, **83**, 271.
WALLGREN, A. (1926): *Acta radiol. (Stockh.)*, **7**, 595.
WILLIAMS, H., and ANDERSON, C. M. (1953): *Quart. J. Med.*, **22**, 295.

APPENDIX

Case No.	*Sex*	*Age (years)*	*Area involved by collapse*	*Duration of collapse (months)*	*Bronchoscopic findings*	*Final X-ray appearance*	*Bronchogram*	*Residual symptoms*
(1) S.B.	f.	9	R.U.L.	6	—	Normal	Crowding and proximal dilatation Normal periphery	None
(2) M.B.	f.	2	R.M.L.	10	—	Fibrosis	Bronchiectasis right middle lobe	None
(3) M.B.	m.	3	R.M.L. and U.L.	5	—	Nil	Nil	None
(4) E.B.	f.	5	R.U.L.	7	Endobronchial granulations	Dense collapse	Bronchiectasis right upper lobe	None
(5) K.B.	m.	9	R.U.L.	5	—	Nil	Nil	None
(6) J.B.	f.	7	R.M.L.	6	—	Fibrosis	Crowding and bronchiectasis	Cough
(7) S.C.	f.	6	R.U.L.	3	—	Nil	Minimal bronchiectasis	None
(8) J.C.	m.	2	R.M.L.	5	—	Extensive calcification	Crowding and irregularity	None
(9) R.C.	f.	4	L.U.L. and L.L.L.	6	Endobronchial granulations	Fibrosis	Bronchiectasis left upper lobe	Cough
(10) M.C.	f.	6	R.M.L. and L.L.	32	Extrinsic pressure	Partial collapse	Bronchiectasis R.M.L. and L.L.	None
(11) M.C.	m.	6	R.M.L. and R.U.L.	14/4	Endobronchial granulations	Streaky collapse	Bronchiectasis right upper lobe	None
(12) M.C.	m.	8	R.L.L.	4	Endobronchial granulations	Collapse	Bronchiectasis right lower lobe	None
(13) B.C.	f.	14	R.M.L.	8	Endobronchial granulations	Nil	Nil	None
(14) J.C.	m.	1	R.U.L.	5	—	Linear collapse	Bronchiectasis right upper lobe	None
(15) E.E.	m.	9	R.U.L.	3	Extrinsic pressure	Nil	Minimal irregularity and dilatation of one branch	None
(16) F.D.	m.	2½	R.M.L.	5	—	Nil	Nil	None

(16) F.D.	m.	2½	R.M.L.	5	—	Nil	one branch Nil	None
(17) J.D.	f.	7	L.U.L.	14	—	Fibrosis	Bronchiectasis left upper lobe	None
(18) B.D.	m.	7	L.U.L.	8	—	Fibrosis	Minimal widening of one apical branch	None
(19) M.F.	m.	8	R.U.L.	14	Narrowing by extrinsic pressure	Extensive calcification	Irregularity of apical branch	None
(20) S.F.	f.	2	L.U.L.	6	—	Nil	Nil	None
(21) C.G.	m.	1½	L.L.L.	8	—	Nil	Nil	None
(22) R.G.	m.	2	L.U.L.	3	—	Nil	Nil in affected segment but bronchiectasis in L.L.L. and lingula	Cough and sputum
(23) C.H.	m.	1½	R.L.L. R.M.L.	5 12	Endobronchial granulations	Nil	Crowding right middle lobe only	Cough
(24) A.H.M.	f.	3	R.U.L.	12	—	Fibrosis	No bronchiectasis; incomplete filling of involved branch	None
(25) J.H.	f.	2	R.U.L.	3	—	Nil	Nil	None
(26) C.H.	m.	3	L.U.L.	11	—	Fibrosis	Nil	None
(27) R.H.	m.	4	L.U.L.	8	—	Fibrosis	Nil	None
(28) D.H.	m.	2	R.U.L.	15	Extrinsic pressure	Nil	Bronchiectasis and stenosis	None
(29) J.H.	m.	7	R.M.L.	18	—	Collapse	Bronchiectasis right middle lobe	Attack bronchitis
(30) C.M.H.	m.	7	R.M.L.	7	Normal	Nil	Irregularity only	None
(31) J.I.	f.	8	R.U.L.	3	—	Collapse	Irregularity	None
(32) G.J.	f.	1	R.U.L./L.L.L.	10/7	—	Partial collapse L.L.L.	Crowding R.U.L. Mild bronchiectasis L.L.L. with stenosis left main bronchus	Bronchitis
(33) C.J.	f.	2	R.U.L.	9	—	Collapse	Failure of affected segment to fill	None
(34) R.K.	m.	16	R.M.L.	10	—	Extensive calcification	Crowding and slight irregularity	Dry cough
(35) R.L.	m.	9	L.U.L.	10	—	Fibrosis	Nil	None
(36) R.L.	m.	8	R.M.L.	10	—	Nil	Nil	None
(37) D.L.	f.	5	R.L.L.	8	—	Nil	Irregularity only	None

APPENDIX (*continued*)

Case No.	*Sex*	*Age (years)*	*Area involved by collapse*	*Duration of collapse (months)*	*Bronchoscopic findings*	*Final X-ray appearance*	*Bronchogram*	*Residual symptoms*
(38) W.M.	m.	6	R.U.L.	4	—	Fibrosis	Diverticulum	None
(39) P.M.	m.	4	L.U.L.	10	Constriction left upper lobe	Fibrosis	Bronchiectasis one branch left upper lobe	None
(40) A.M.	m.	6	R.M.L.	6	Endobronchial granulations	Nil	Crowding right middle lobe	None
(41) J.M.	m.	6	L.U.L.	5	—	Some collapse	Nil	None
(42) H.M.	m.	5	L.U.L.	8	—	Collapse	Irregularity and crowding	None
(43) J.M.	f.	6	R.M.L./R.L.L.	17/3	—	Collapse	Dilatation and crowding R.M.L.	Cough and sputum
(44) T.M.	m.	9	R.U.L.	7	—	Nil	Nil	None
(45) J.M.	m.	12	R.U.L.	9	Extrinsic pressure	Collapse	Bronchiectasis right upper lobe	None
(46) M.N.	m.	5	L.U.L.	8	Endobronchial granulations	Nil	Nil	None
(47) V.N.	m.	3	L.U.L.	9	—	Fibrosis	Nil	None
(48) J.P.	m.	15	R.M.L.	17	Extrinsic pressure	Collapse	Bronchiectasis right middle lobe	Cough and sputum (lobectomy)
(49) R.P.	m.	9	R.M.L.	3	—	Nil	Crowding	Nonspecific infection in collapsed lobe
(50) S.P.	f.	5	R.U.L.	6	—	Collapse	Bronchiectasis and stenosis	None
(51) E.P.	f.	3	R.M.L.	8	—	Collapse	Crowding	None
(52) P.P.	f.	3	Left lingula	18	—	Nil	Bronchiectasis of lingula at origin	None
(53) M.R.	m.	8	R.M.L./R.L.L.	8	—	Collapse	Bronchiectasis right lower lobe Crowding R.M.L.	None

(54) V.R.	f.	3	L.U.L.	12 total 6 partial	Normal	Fibrosis	Bronchiectasis left upper lobe	None (lobectomy)
(55) L.S.	f.	6	L.U.L.	4	—	Nil	Nil	None
(56) S.S.	f.	2½	R.M.L.	11	—	Fibrosis	Bronchiectasis right middle lobe	Nonspecific infection in collapsed segment
(57) L.S.	f.	5	R.U.L.	26	Congestion only	Collapse	Bronchiectasis and stricture	None
(58) S.S.	m.	5	R. dorsal lobe	8	No abnormality	Collapse and fibrosis	Bronchiectasis	None
(59) B.T.	m.	6	R.M.L./L.L.	12	Endobronchial granulations	Patchy collapse	Bronchiectasis right middle lobe	Cough (lobectomy)
(60) R.T.	m.	7	R.M.L.	8	Extrinsic pressure	Fibrosis	Nil	None
(61) S.T.	m.	4	L.L.L.	7	Endobronchial granulations	Nil	Irregularity only	None
(62) C.T.	f.	8	L.U.L.	12	Normal	Nil	Nil	None
(63) T.V.	m.	12	R.U.L.	3	Endobronchial granulations	Nil	Nil	None
(64) L.W.	m.	13	R.M.L.	7	—	Streaky collapse	Bronchiectasis R.M.L. and anterior basal segment	Bronchitis
(65) R.W.	m.	7	L.U.L. and lingula	5	—	Slight fibrosis	Nil	None
(66) M.W.	m.	2	R.M.L.	5	—	Slight fibrosis	Crowding only	None
(67) M.W.	f.	2	L.U.L.	9	—	Fibrosis	Nil	None
(68) A.W.	f.	4	L.U.L.	11	Œdema	Collapse	Bronchiectasis left upper lobe	Upper respiratory infection
(69) V.W.	f.	2	R.U.L.	4	—	Collapse	Bronchiectasis right upper lobe	None
(70) I.W.	f.	5	L.U.L.	4	—	Nil	Bronchiectasis L.U.L. and irregularity of lingula	None
(71) C.Y.	f.	6	L.L.L.	3	—	Collapse	Nil	None

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TUBERCULIN REACTIONS AND B.C.G. VACCINATION IN OLD AGE

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The chief problem of pulmonary tuberculosis now stands in relation to the elderly male. There has not been such a marked change in the age incidence among females, although many old women with tuberculosis are now to be found in sanatoria. Various reasons have been advanced for this shift of the incidence of tuberculosis towards old age. Certainly self-neglect and living alone play a major part in the breakdown of pre-existing lesions. However, some of these elderly patients have an X-ray appearance of acute disease of recent origin, and it has been suggested (Kinsella, 1957) that this may be a manifestation of fresh infection in a tuberculin negative subject. A primary complex can occur at an advanced age (Kayne *et al.*, 1948). A tuberculin-negative subject exposed to infection risks disease, and modern practice in the control of tuberculosis recommends B.C.G. vaccination of contacts of all ages who are tuberculin-negative (Heaf, 1956). Various authors have stated that tuberculin sensitivity declines with increasing age (Stieglitz, 1954; Giannini and Sloan, 1957; Heaf, 1955; Caplin *et al.*, 1958; Griep and Bleiker, 1957), and Robins *et al.*, (1954) gave a 5 per cent. decrease per decade after 60, until at the age of 80 only 50 per cent. were tuberculin-positive.

One of the factors in the incidence of acute tuberculosis in the elderly may be a negative tuberculin state. When a new case of tuberculosis is discovered more attention should be paid to the elderly contacts. A chest X-ray and a tuberculin test is just as applicable in the protection of an old person as in a child contact and B.C.G. vaccination may be equally necessary. Thought should also be given to the protection of geriatric patients who may come in contact with tuberculous patients in the same hospital. In order to discover the incidence of negative reactors to tuberculin among the elderly in this part of England a tuberculin survey was carried out on a large number of patients in geriatric wards. A group of negative reactors who were thought to be exposed to possible tuberculous infection were then given a protective B.C.G. vaccination. This paper describes the tuberculin sensitivity of 1,000 elderly patients and the results of protective vaccination of 101 negative reactors.

Method

The tuberculin testing in this investigation was carried out by the Multiple Puncture method, using the Heaf apparatus (Heaf, 1953) and the appropriate solution of P.P.D. (strength 100,000 units Old Tuberculin/ml.) issued by the Ministry of Health. All the tests and readings after 72 hours were carried out by one observer. The needles of the apparatus were set to penetrate the skin

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2 mm. The test was speedily performed, there were no local complications, and the reactions were simple to interpret.

Results

The results of the investigation are shown in Table 1.

Table 1

Age groups	60-64	65-69	70-74	75-79	80-84	85-89	90+
Total number tested	63	111	166	260	233	127	42
Number positive ..	53	82	118	180	156	88	32
Per cent. positive ..	84	74	71	69	67	69	76
Males							
Number tested ..	27	46	71	86	61	34	7
Number positive ..	23	37	50	64	44	22	5
Per cent. positive ..	85	83	70	74	72	65	71
Females							
Number tested ..	36	65	95	174	172	93	35
Number positive ..	30	45	68	116	112	66	27
Per cent. positive ..	83	69	71	67	65	71	77

It will be seen that there is no significant variation in the percentage of positive reactors over the age of 65 in the different age groups or between the sexes. The intensity and size of the local reaction did not show any diminution with increasing age. However, there was variation in the percentage of positives when compared with population densities (Table 2).

Table 2

Area	*Description*	*Population density per built-up acre*	*Number examined*	*Per cent. positive*
Ilkley ..	Rural and residential	10	139	57
Skipton ..	Market town	15	129	68
Keighley ..	Industrial town	28	147	71
Leeds ..	Highly industrialised city	77	586	75

The patients examined in the various hospitals in the survey were, for the most part, natives of the catchment area of that particular hospital.

A record was made of the main diagnosis of each patient tested, and the results of the tuberculin test in seven diagnostic groups show little variation (Table 3). These are easily selected groups and are not the total number examined.

No patient was excluded because of severe illness, and only patients who were obviously moribund and likely to die within hours were not tested. No known cases of pulmonary tuberculosis were included in the investigation.

TABLE 3

Diagnosis	*Number tested*	*Per cent. positive*
Hemiplegia	137	76
Diabetes	30	80
Arthritis	65	74
Bronchitis	58	66
Senility and senile dementia ..	102	70
Fractures	27	78
Cancer	40	67

B.C.G. VACCINATION

A Ministry of Health Circular (7/58) on B.C.G. recommends vaccination of any persons who are considered to be at special risk because of contact with patients. It was felt that ambulant geriatric patients in sanatoria and hospitals still containing tuberculous infective patients were at risk, and came within the category of persons to be protected by B.C.G. vaccination.

The only reference in the literature to the use of B.C.G. in old age (Palitz and Aronsohn, 1957) describes the vaccination of ten tuberculin-negative old people, who all developed the typical local reaction and became Mantoux-positive. In this investigation 101 B.C.G. vaccinations were carried out; in 28 the Danish liquid vaccine and in 73 the British freeze-dried vaccine was used.

It is known that B.C.G. vaccination in a tuberculin-positive patient produces an accelerated reaction at the site of vaccination. There is local redness and swelling after four days, and a maximal reaction after fourteen days, often with ulceration; at twenty-eight days the lesion has almost healed. A tuberculin-negative patient, when vaccinated with B.C.G., shows only a minimal reaction after four days and the local lesion is approaching its maximum after twenty-eight days. However, a patient whose tuberculin test is negative because of waning allergy but who has previously been infected may be re-sensitised by B.C.G. vaccination (Jonsen and Ustvedt, 1950). He then develops an accelerated reaction (Palitz and Aronsohn, 1957) at the vaccination site, and the original tuberculin test may become positive owing to local persistence of tuberculin (Pepys, 1955).

METHOD

B.C.G. vaccination was carried out over the left deltoid muscle, the site was inspected after four days to detect accelerated reactions, re-examined after fourteen days if there was doubt, and finally examined after twenty-eight days. The size of the lesion was measured, the local lymph nodes were palpated for enlargement and the Heaf Multiple Puncture test was repeated. Patients who remained tuberculin-negative after apparently successful vaccination were tested again after eight and twelve weeks to detect late conversion.

RESULTS

It was inevitable when dealing with geriatric patients that several deaths

and discharges occurred which made a complete follow-up impossible during the relatively lengthy period of the investigation. The results are seen in Table 4.

TABLE 4

	Danish liquid vaccine	*British freeze-dried vaccine*
Number vaccinated	28	73
Accelerated reactions	7	8
Normal reactions	21	65
Average diameter of lesion after 28 days	8 mm.	8 mm.
Tuberculin test after 1 month	17 positive 17 tested (100%)	53 positive 60 tested (88%)
Tuberculin test after 2 months	—	1 positive 6 tested
Tuberculin test after 3 months	—	1 positive 4 tested
Conversion rate 3 months after vaccination	100%	92%
Failures to convert after vaccination	none	3
Untraced or died	4	8

In the group of 28 patients who received Danish liquid vaccine there were seven accelerated reactions. The remaining 21 patients had normal reactions but 4 died before re-testing with tuberculin. The 17 survivors were all Mantoux-positive twenty-eight days after vaccination. There were no severe local reactions to B.C.G., a dressing was required in only one patient, and in no case was there palpable enlargement of the regional lymph nodes. The average size of the B.C.G. lesion at twenty-eight days was 8 mm.

In the group of 73 patients vaccinated with British freeze-dried B.C.G. there were eight accelerated reactions. There were sixty-five normal reactions but only sixty were available for tuberculin testing after one month. Fifty-three out of sixty were positive. One late conversion was found in six negatives re-tested at two months, and one further late conversion out of four tested at three months after apparently successful vaccinaton. It was known that three out of sixty-five successful vaccinations failed to become tuberculin-positive, but in each of these three patients the local reaction to B.C.G. had been only 4 mm. in diameter. The average size of the lesions in the others was 8 mm. in diameter. There were no complications with freeze-dried B.C.G. and it was noted that there was less local irritation, less reddening, and the local lesion appeared somewhat milder than that produced by Danish liquid vaccine. In the total of 101 vaccinations, the original negative multiple puncture test was seen to become spontaneously positive after B.C.G. in six patients.

Discussion

The multiple puncture tuberculin test is known to be as reliable or more reliable than the intradermal injection of tuberculin (Stewart *et al.*, 1958; B.T.A. Report, 1958). A small number of preliminary intradermal tests were carried

out, and the method was found to be difficult and slow owing to the thinness of the atrophic skin of old age. Also several unpleasant hæmorrhagic reactions took place when the patient was tuberculin positive. The multiple puncture test was simple and quick and the most practicable for testing large numbers.

The percentage of positive reactors was remarkably constant at all ages. There was no evidence of an increasing percentage of negative reactors with increasing age. In fact, the nonagenarians showed a high degree of allergy, perhaps evidence that their protective mechanisms are in good order. A previous survey (Beresford, 1958) of over 1,000 geriatric patients using the intradermal test also showed an almost uniform level of tuberculin sensitivity in all age groups over 65. It seems likely that some of the figures quoted by various authors showing declining sensitivity with increasing age are based on too small a number of patients. This is not to say that there is not a decline in some patients. Chest X-rays of aged tuberculin-negative patients (Amazon, 1943) may show calcified tuberculous lesions. The accelerated reactions and re-sensitising effect of B.C.G. seen in this investigation are evidence of waning allergy but occurred in all the 5-year age groups quite uniformly and were not more common in the older patients. The idea of an agewise decline of tuberculin sensitivity is not supported by the facts of this survey, and belongs to the erroneous concept that because a patient is aged his reactions to external stimuli inevitably become depressed.

There is no significant difference in the tuberculin reaction between males and females, and the clinical diagnosis apparently has no influence on the tuberculin test. The decreasing number of positive reactors in the less densely populated areas is in keeping with the fact that there is less tuberculous infection when there is no overcrowding. It is interesting to note that Beresford (1958) found a uniform level of about 60 per cent. tuberculin positives in geriatric patients in Dorset, which is not densely populated, while in this survey in the West Riding of Yorkshire the figure is about 70 per cent.

B.C.G. vaccination presented no difficulties and there were no severe reactions. The results using Danish liquid vaccine were slightly better than the British freeze-dried vaccine, but the convenience of the latter was a great advantage. Delay in Mantoux conversion has been reported in infants and children (Lorber *et al.*, 1956; Rosenthal, 1952) with freeze-dried B.C.G., and the same phenomenon was seen in a small number of the geriatric patients. Accelerated reactions following B.C.G. vaccination were not accompanied by general symptoms and the local inflammation was not sufficiently severe to upset the patient. There is no need to fear ill effects from unwittingly producing an accelerated reaction. No observations have yet been made on the duration of Mantoux conversion following B.C.G. in geriatric patients, but, in view of the satisfactory immediate conversion achieved, we feel this is a worthwhile protective measure for the elderly contact of tuberculosis.

Summary

Tuberculin testing by the multiple puncture method of 1,000 geriatric patients showed that there is no waning of tuberculin sensitivity with increasing

age. Clinical diagnosis does not affect the tuberculin reaction. Increased population density produces a higher percentage of positive reactors.

One hundred and one B.C.G. vaccinations were carried out on negative reactors using Danish liquid vaccine and British freeze-dried vaccine. The procedure in geriatric patients is found to be safe and effective in producing Mantoux conversion.

We would like to thank Dr. W. S. Suffern, who allowed us access to his patients, and the nursing staff of the geriatric hospitals in the area who willingly assisted in this investigation.

REFERENCES

AMAZON, P. (1943): *Amer. Rev. Tuberc.*, **47,** 41.
BERESFORD, O. D. (1958): *Amer. Rev. Tuberc.*, **77,** 323.
BRITISH TUBERCULOSIS ASSOCIATION REPORT (1958): *Tubercle (Lond.)*, **39,** 76.
CAPLIN, M., SILVER, C. P., and WHEELER, W. F. (1958): *Tubercle (Lond.)*, **39,** 84.
GIANNINI, D., and SLOAN, R. S. (1957): *Lancet*, **1,** 525.
GRIEP, W. A., and BLEIKER, M. A. (1957): *Tubercle (Lond.)*, **38,** 259.
HEAF, F. R. G. (1955): *J. roy. Inst. publ. Hlth.*, **18,** 324.
(1956): *Brit. med. J.*, **2,** 1383.
(1953): *Tubercle (Lond.)*, **34,** 335.
JONSEN, J., and USTVEDT, H. J. (1950): *Tubercle (Lond.)*, **31,** 261.
KAYNE, G. G., PAGEL, W., and O'SHAUGHNESSY, L. (1948): "Pulmonary Tuberculosis." Oxford University Press.
KINSELLA, T. J. (1957): *Geriatrics*, **12,** 355.
LORBER, J., HART, C. B. S., FARMER, P., and MUGGLETON, P. W. (1956): *Tubercle (Lond.)*, **37,** 187.
Ministry of Health Circular 7/58.
PALITZ, L. S., and ARONSOHN, M. H. (1957): *Amer. Rev. Tuberc.*, **75,** 461.
PEPYS, J. (1955): *Amer. Rev. Tuberc.*, **71,** 49.
ROBINS, A. B., ABELES, H., ARONSOHN, M. H., GLASS, R., GOLDBERG, S., KONTERWITZ, H., LEVINE, I., and SCHWARTZ, S. (1954): *Amer. Rev. Tuberc.*, **69,** 1057.
ROSENTHAL, S. (1952): *Amer. Rev. Tuberc.*, **65,** 344.
STEWART, C. J., CARPENTER, R. G., and MCCAULEY, P. (1958): *Tubercle (Lond.)*, **39,** 143.
STIEGLITZ, L. (1954): "Geriatric Medicine." London: Pitman.

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B.C.G. VACCINATION— A PRELIMINARY COMMUNICATION

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Introduction

Numerous substances have been tried for specific immunisation against tuberculosis, including old tuberculin, and the metabolic products of tubercle bacilli, but none has been of very much value.

Wallgren (1928) advocated the intracutaneous injection of the vaccine, B.C.G., reported by Calmette and Guérin (1908) and initially used orally (Calmette *et al.*, 1924). Pasteur freeze-dried B.C.G. vaccine, modified by Ungar *et al.* (1956), is now generally available. Wells (1937) discovered the mico-bacterium of vole tuberculosis. A live vaccine containing this organism has been tried, but on a much smaller scale than B.C.G. vaccine.

Wallgren (1927) thought that protection was ineffective unless an allergy to tuberculin developed, and it is now believed the protection is closely related to the hypersensitivity reaction elicited by injecting tuberculin intracutaneously.

Few reports in this country exist on the length of time this hypersensitivity and protection persist. We present a preliminary communication on 264 of over 1,000 cases given Danish B.C.G. from the State Serum Institute in Copenhagen since 1950 and followed up for a period of five to eight years.

Vaccination Scheme

The scheme of vaccination in routine use at the East Ham Chest Clinic and modified from Ministry of Health Memorandum 322/BCG and 322/BCG (Revised) (1950) is described on the following page (see table).

Results

The cases consisted of Heaf-negative contacts of tuberculous patients, newborn babies who would have become contacts, and any patient who specifically requested vaccination. Thus there was a wide age range and no close selection as in the Medical Research Council Trial (1956).

We have vaccinated over 1,000 cases with Danish B.C.G. since 1950. This preliminary report is based on 264 of these followed up for five to eight years. The table analyses these cases.

	Years for which Heaf tuberculin test or Mantoux (1 : 1,000) test have remained positive			
Years ..	8	7	6	5
No. of cases	13	82	98	65

Total = 258.

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1. Newborn contacts—vaccinate—repeat Heaf multiple puncture tuberculin test in six weeks and X-ray at two years, then transfer to scheme.
2. Under two years—Heaf tuberculin test only.
3. Over two years—X-ray and Heaf tuberculin test.

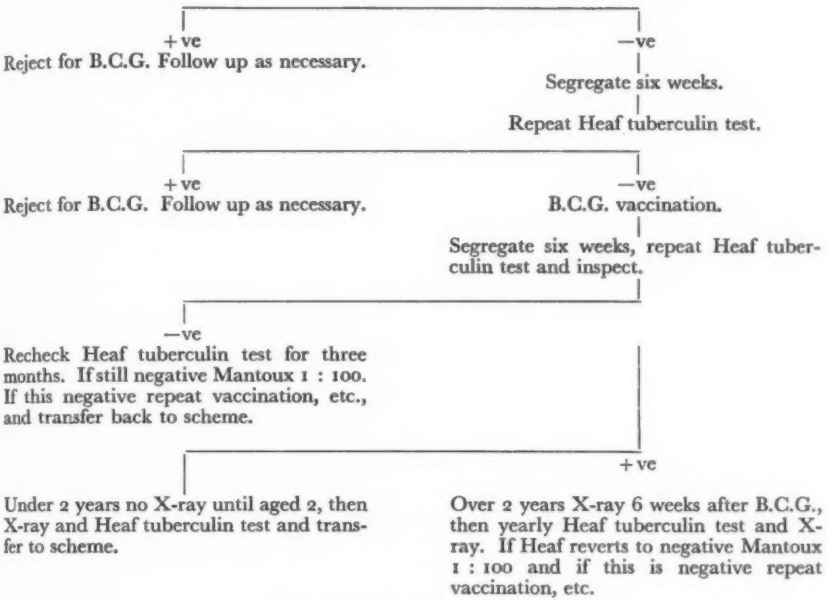
+ve
−ve
Reject for B.C.G. Follow up as necessary.
Segregate six weeks.
Repeat Heaf tuberculin test.
+ve
−ve
Reject for B.C.G. Follow up as necessary.
B.C.G. vaccination.
Segregate six weeks, repeat Heaf tuberculin test and inspect.
−ve
Recheck Heaf tuberculin test for three months. If still negative Mantoux 1 : 100. If this negative repeat vaccination, etc., and transfer back to scheme.
+ve
Under 2 years no X-ray until aged 2, then X-ray and Heaf tuberculin test and transfer to scheme.
Over 2 years X-ray 6 weeks after B.C.G., then yearly Heaf tuberculin test and X-ray. If Heaf reverts to negative Mantoux 1 : 100 and if this is negative repeat vaccination, etc.

TABLE OF VACCINATION SCHEME

In one case aged 11 years conversion did not occur after vaccination, but successful vaccination was subsequently performed. Six cases had to be re-vaccinated, 2 after two years, 3 after three years and 1 after five years. Thus in 97·7 per cent. of cases conversion would appear to have remained positive for a period of five to eight years. Of the 264 cases 33 were newborn infants, who were vaccinated within two weeks of birth. All converted at the initial vaccination and none of these have had to be re-vaccinated.

Since the vaccination and conversion, 85 (36 per cent.) of the 264 cases have been known to have contact, often very close contact, with other members of their family who have subsequently had acid-fast bacilli in the sputum. In 3 of these 85 cases the contact was with relatives from whose sputum atypical chromogenic acid-fast bacilli were isolated. Despite a persistence of conversion, 1 of the 258 cases developed primary pulmonary tuberculosis. He developed an atelectatic right lower lobe and hilar adenopathy. Subsequent chest X-rays showed a calcified lesion in the right lower zone. This patient was a contact of his father who had a positive sputum. Thus 0·39 per cent. developed proven pulmonary tuberculosis.

The only complication of vaccination was local cervical or axillary glandular enlargement, requiring aspiration in three cases.

Discussion

B.C.G. schemes have been followed up in various countries for a substantial number of years, and a few selected reports are reviewed.

In America, Aronson and Palmer (1946), Aronson (1948), Aronson and Aronson (1952) and Stein and Aronson (1953), in a follow-up of 1,551 B.C.G. vaccinated North American Indians, have shown that hypersensitivity was 93·3 per cent. after one year and 90·2 per cent. after eleven years. Aronson and Palmer (personal communication to Irvine, 1957) have followed nearly all of these cases for twenty years. 0·84 per cent. died of tuberculosis, whereas in 1,457 controls 4·7 per cent. died of tuberculosis, *i.e.* 82 per cent. were protected. The cause of death was verified in each case. These figures support a close but not absolute relationship between resistance to infection and hypersensitivity. In another trial by the United States Public Health Service (Palmer and Shaw, 1953) the incidence of deaths from tuberculosis was not found to be higher than in vaccinated groups. Their results, however, relied solely on the established system of notification of tuberculosis cases. Rosenthal *et al.* (1957) (quoted in Rosenthal, 1957) have found that a positive tuberculin reaction remains from two to three years in 80 per cent. of young adults after B.C.G. vaccination and that in non-segregated newborns the reversion rate was 11 per cent. at five years and 27 per cent. after eight years.

In Scandinavia, Dahlstrom and Difs (1951) and Dahlstrom (1953) in a retrospective study of Swedish conscripts offered B.C.G. vaccination on entering the army, found the vaccine did not appear to confer protection against primary tuberculosis until two months had elapsed, nor against other forms of tuberculosis for six months. The incidence of primary tuberculosis from six months to five years after vaccination was 1·7 per cent. in favour of the vaccinated, *i.e.* 86 per cent. were protected. Hyge (1956) followed up 368 adolescent girls exposed to a school mistress with open tuberculosis. After twelve years, 2 of 106 given B.C.G. vaccination and 14 of 94 controls developed post-primary tuberculosis. Forty-one of the controls developed primary tuberculosis. Heimbeck (1929) reduced the incidence of tuberculosis in pupil nurses from 29·6 per cent in the tuberculin negative to 2·3 per cent. in those vaccinated with B.C.G., thus protecting 83 per cent. Enell (1955) has shown that in infants vaccinated at birth with attenuated Swedish vaccine, 85 per cent. were still positive to tuberculin testing after seven years. Wasz-Hockert and Donner (1953) found the reversion rate in vaccinated children protected from super-infection to be 7·5 per cent. for the first year, 15 per cent. for the second and 29·5 per cent. for the third.

In Ireland Cowell (1952) has followed cases given B.C.G. under the National B.C.G. scheme in Ireland. Of 107 cases vaccinated in infancy and early childhood a constant 91 per cent. gave positive tuberculin reactions three to six years after vaccination. Cowell (1957) states that 37,000 patients have been vaccinated in Ireland. In one group of these in Dublin followed for thirteen years, 8·4 per cent. reverted their tuberculin test, and in another group in County Sligo 12 per cent. reverted.

In England the Medical Research Council in their first progress report

(1956) have shown that of 13,200 adolescent controls aged 14 to 15½ years, 1·94/1,000 developed tuberculosis, whereas of 14,100 vaccinated with B.C.G. 0·37/1,000 developed tuberculosis, *i.e.* 81 per cent. were protected. In the trial both B.C.G. and vole vaccination conferred protection within six months, and remained substantial between two and two-and-a-half years after vaccination. Supplementary incomplete information suggests protection is maintained for four years. Gaisford (1955) using several vaccines, including standing Danish B.C.G., in newborn infants found this last gave quickest Mantoux conversion. Although theoretically the vaccine does not exert its influence for some time, his practical experience demonstrated some value during the first six months, and protection may start before conversion and even persist after reversion. After four years he found the number of reversions "extremely small." Animal experiments using vole bacilli have shown definite resistance after allergy has disappeared. The same may apply to B.C.G. vaccination (Irvine, 1949).

Rollof *et al.* (1954) found that newborn infants of tuberculous mothers were slow to respond to B.C.G. vaccination and that they reverted more readily, suggesting a passively transmitted immunity exists. Gaisford (1955) found the percentage of infants converting within four weeks was higher in the contact than non-contact cases. In our 33 newborn cases we have noted delay in conversion in some, but all were successfully vaccinated the first time and none have so far needed re-vaccination.

Wells and Wylie (1951), using vole bacilli, found that of 2,500 vaccinated 0·08 per cent., and of 717 controls, 2·37 per cent., developed tuberculosis, four in the latter group died, *i.e.* 97 per cent. protection. In the Medical Research Council Trial (1956) of 6,400 vaccinated with vole bacilli, and a similar number of tuberculin negative controls, the incidence was 0·44 and 2·06/1,000 respectively, *i.e.* 79 per cent. protected.

The overall picture appears to be that protection by B.C.G. vaccination varies from 81 per cent. (M.R.C. Trials 1956) to 95 per cent. (Hyge, 1947). Using vole bacilli the variation is 79 per cent. (M.R.C. Trials 1956) to 97 per cent. (Wells, 1937).

The tuberculin reversion rates after vaccination have been followed for up to thirteen years in various countries, but in this country for only two-and-a-half years so far, and in a selected age group. Although the number of cases in our preliminary report is not great it does show a very small tuberculin reversion rate after five to eight years and covers a comprehensive age range.

To obtain accurate figures it is necessary to prevent infection by virulent tubercle bacilli of the vaccinated persons under observation. Tuberculous infection would increase tuberculin sensitivity if the sensitivity conferred by B.C.G. were declining (Heaf and Rusby, 1959). In our cases no segregation was carried out after vaccination and conversion. It is possible that some of the 97·7 per cent. of cases remaining tuberculin positive for five to eight years could have become negative and then developed subclinical primary tuberculosis between their annual Heaf tests and chest X-rays. This would imply that the figure of 97·7 per cent. is too high. Similar inaccuracies would apply to most other follow-up series. The 0·39 per cent. incidence of tuberculosis in

our cases is low considering 85 of them had close contact with open cases of pulmonary tuberculosis. Of 145 millions vaccinated with B.C.G. only four deaths have occurred, and this compares favourably with deaths from smallpox vaccination in England and Wales. Of over 30,000 vole vaccinations there have been no deaths (Irvine, 1957).

Summary and Conclusions

Of 264 cases given B.C.G. vaccination since 1950, 97·7 per cent. appear to have maintained their hypersensitivity for a period of five to eight years. This high figure may be partially due to 36 per cent. of the cases having close contact with relatives known to have acid-fast bacilli in their sputum. To obtain more accurate figures for the length of time conversion lasts, vaccinated cases should ideally be segregated from patients with active tuberculosis. The incidence of proven primary tuberculosis despite persisting positive tuberculin tests was 0·39 per cent. This figure coincides with the results of previously published series. A further report on the remainder of our cases when observed for an adequate period will follow.

We wish to thank Sister F. M. Williams and her staff for their help and assistance in following up these cases, and Professor F. R. G. Heaf for his most helpful criticism.

Addendum

Since writing this paper a case has come to our notice who was vaccinated in 1950 and known to be tuberculin sensitive in 1952. She subsequently failed to co-operate with her follow-up and was thus excluded from the survey. In 1959 she was found to have active pulmonary tuberculosis and was tuberculin sensitive. Her state of sensitivity prior to the onset of the tuberculosis is not known, but it is realised that if she had remained positive our incidence of tuberculosis would increase to 0·77 per cent. It is just possible that other such cases may exist which would further increase the figure.

References

Aronson, J. D. (1948): *Amer. Rev. Tuberc.*, **58**, 255.
Aronson, J. D., and Aronson, C. F. (1952): *J. Amer. med. Ass.*, **149**, 334.
Aronson, J. D., and Palmer, C. E. (1946): *Pbl. Hlth Rep. (Wash.)*, **61**, 802.
Calmette, A., and Guérin, C. (1908): *C.R. Acad. Science*, **147**, 334.
Calmette, A., Guérin, C., and Weill-Halle, B. (1924): *Bull. Acad. Méd.*, **91**, 787.
Cowell, J. St. P. (1952): *Irish J. med. Sci.*, **320**, 358.
(1957): *J. Irish med. Ass.*, **241**, 4.
Dahlstrom, G. (1953): *Acta tuberc. scand.*, Suppl. 32.
Dahlstrom, G., and Difs, H. (1951): *Ibid.*, Suppl. 27.
Enell, H. (1955): *Acta paediat. (Uppsala)*, **44**, Suppl. 101.
Gaisford, W. (1955): *Brit. med. J.*, **2**, 1164.
Heaf, F. R. G., and Rusby, N. L. (1959): "Recent Advances in Respiratory Tuberculosis." London: Churchill.
Heimbeck, J. (1929): *Ann. Inst. Pasteur*, **43**, 1229.
Hyge, T. V. (1956): *Acta tuberc. scand.*, **22**, 89.
Irvine, K. N. (1949): "B.C.G. Vaccination in Theory and Practice." Oxford: Blackwell.
(1957): "B.C.G. and Vole Vaccination." London: N.A.P.T.
Medical Research Council, 1st Progress Report (1956): *Brit. med. J.*, **1**, 413.

MINISTRY OF HEALTH MEMORANDUM (1950): 322/BCG and 322/BCG. (Revised.)
PALMER, C. E., and SHAW, L. W. (1953): *Amer. Rev. Tuberc.*, **68,** 695.
ROLLOF, S., LAGERCRANTZ, R., and LIND, J. (1954): *Acta paediat.* (*Uppsala*), Suppl. 100, 179.
ROSENTHAL, S. R. (1957): "B.C.G. Vaccination against Tuberculosis." London: Churchill.
STEIN, S. C, and ARONSON, J. D. (1953): *Amer. Rev. Tuberc.*, **68,** 462.
UNGAR, J., FARMER, P., and MUGGLETON, P. N. (1956): *Brit. med. J.*, **2,** 568.
WALLGREN, A. (1927): *Acta paediat.* (*Uppsala*), **7,** 120.
(1928): *J. Amer. med. Ass.*, **91,** 1876.
WASZ-HOCKERT, O., and DONNER, M. (1953): *Bull. Hyg.*, **28,** 1036.
WELLS, A. Q. (1937): *Lancet*, **1,** 1221.
WELLS, A. Q., and WYLIE, J. A. H. (1951): *Brit. med. Bull.*, **10,** 96.

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BRONCHIOLITIS AFTER SHOT FIRING IN A COLLIERY

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Gassing by nitrous fumes or the oxides of nitrogen is a well-known risk in industry: in processes where dilute nitric acid comes into contact with metals, when there is incomplete combustion of nitrogenous compounds, or in welding processes where the electric spark acts on the nitrogen of the atmosphere.

Such hazards occur less in industries where experience has shown how they may be avoided or prevented, while fresh hazards appear where new techniques are being evolved. For example, in the Cleveland hospital disaster of 1929 over 100 fatal cases occurred following the inhalation of nitrous fumes from the slow combustion of great quantities of X-ray films of the nitrocellulose type (Nichols, 1930). The use of a non-inflammable material, cellulose acetate, for X-ray films has avoided another disaster of this kind. Grain silos have recently been shown as a risk to agricultural workers, and other risks of poisoning by nitrous fumes are likely to come and go. The most common sequel of inhalation of these fumes in high concentration is pulmonary œdema, which is fatal in a great number of cases within a period from several hours to three days after exposure. Less severe exposure often leads to broncho-pneumonia or bronchiolitis, usually after a longer or shorter interval. Lange (1901) first drew attention to the pathological entity of bronchiolitis fibrosa obliterans in a report of two fatal cases in whom the disease was of unknown origin. In the following year Fraenkel (1902) described a fatal case of bronchiolitis fibrosa obliterans in a brass dipper, due to nitrous fumes, and discussed all aspects of differential diagnosis. As the gross pathological picture was similar to that of miliary tuberculosis he stressed the importance of the differential diagnosis from the point of view of industrial insurance. Since then a number of pathological and clinical studies of bronchiolitis due to industrial hazards have been recorded. Recently Darke and Warrack (1958) described two cases of bronchiolitis from nitrous fumes.

Modern mining is an industry that has successfully learned how to diminish the risks of nitrous fumes. Nevertheless, the danger has not completely disappeared, and Lechner (1954) described four cases of poisoning by nitrous fumes —three of them fatal—which occurred in mining galleries during the construction of power stations in the Tyrol and Vorarlberg in Austria between 1949 and 1954. In South Africa Becklake *et al.* (1957) examined five gold miners who had, very remarkably, recovered from an episode of acute pulmonary œdema following exposure to nitrous fumes during a blasting operation underground. They were followed up for sixty-four months and four of them complained of impairment of their physical fitness on exertion. Pulmonary function tests revealed impairment of respiratory function, and the authors

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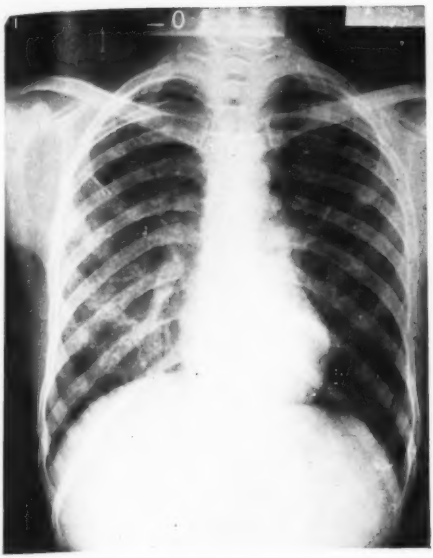

FIG. 1.—Case 1. Chest radiograph on 10.5.57, over four weeks after exposure, showing opacities throughout both lungs.

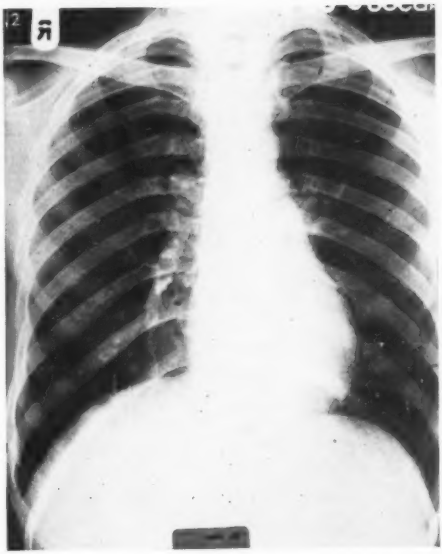

FIG. 2.—Case 1. Clearing shown on 31.5.57.

FIG. 3.—Case 2. Chest radiograph on 10.5.57, showing opacities in middle and lower zones.

FIG. 4.—Case 2. Clearing shown on 24.5.57.

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concluded that these men had some degree of bronchial or bronchiolar narrowing following acute bronchiolitis.

In Britain H.M. Chief Inspector of Mines and Quarries in his annual reports from 1948 to 1956 (Mines), and 1957 (Mines and Quarries), records no accident of this type. However, two casualties after shot firing in a Northumbrian coal mine occurred in 1957.

Case Reports

The details of the following cases were obtained after the end of the acute stage of their illness.

Case 1. A shot firer, aged 30, was referred to the chest clinic on May 10, 1957. The previous day a preliminary diagnosis of pulmonary tuberculosis had been made in the out-patient department of a large general hospital. At the beginning of April, in a spell of hurried work during the morning shift, he fired four shots simultaneously, using " Unigel " as an explosive, at a distance of 30 to 40 yards (27-37 metres). He returned immediately for the electric coupling of four further shots, this in disregard of the regulations. There was poor ventilation and the approach was difficult. He asked a workmate for help, but this man could not manage the approach and returned half way. The place was filled with hot dust and fumes which could not escape. The shot firer's eyes were watering, his nose was running and he felt a burning sensation in the chest. He finally reached the shot holes and made the connections. He again fired at a distance of 30 to 40 yards. He finished his shift with difficulty, often having to sit down and rest. He stayed off work three days and improved, but on return to work he did not feel fully fit. From May 6 he began to bring up small clots of blood, felt weak, and his condition deteriorated during the following days. On May 10 at the chest clinic, where he was brought as a stretcher case, he appeared breathless, cyanosed and ill. A radiograph showed opacities of a nodular type densely distributed throughout both lungs but more marked in the right lung, suggestive of pulmonary tuberculosis (Fig. 1)*. He was admitted to hospital on May 11, when his temperature was 100·4° F. (38° C.) and the pulse rate 110/min. A few moist sounds were heard over both lungs. The heart was normal and the blood pressure 140/80 mm. Hg. Treatment with 300 mgm. of isoniazid and 1 gm of streptomycin daily was immediately started.

All sputum examinations, including cultures, proved negative for tubercle bacilli; no fungi were found in the sputum. The white cell count was 17,900 per c. mm. with 93% neutrophils, 5% lymphocytes, 1% monocytes and 1% eosinophils. The erythrocytes showed normal morphology, hæmoglobin was 98%. The plasma protein concentration was 6 g. % with 3·3% albumin and 2·7% globulin. Tuberculin skin test (Heaf's multiple puncture test) was positive.

During the following three days the temperature increased to a maximum of 101·6° F. (38·7° C.) and then decreased gradually, but the patient showed no improvement. He was very breathless and cyanosed; squatting in bed eased his distress. Numerous moist sounds were heard over both lungs but were more marked in the left lung. He still brought up blood-stained sputum. On May 18 he was given 5 mg. of Prednisolone, on the 19th two doses, and from May 20, 5 mg. three doses daily. He improved gradually and his dyspnœa

* The figure numbers in the text refer to Plate XLV.

decreased. On May 24 a radiograph showed considerable clearing of the lungs and at that time the patient's general condition had much improved. On May 31 both lung fields appeared almost clear radiographically (Fig. 2). By this time the E.S.R. had fallen from 95 mm. on admission to 7 mm. at one hour (Westergren). The patient's further progress was entirely satisfactory and he resumed work in August 1957. He was seen repeatedly at the clinic, the last time in February 1959.

CASE 2. On the same May 10, 1957, the colliery deputy (foreman), aged 57, was referred to the clinic by his family doctor, who was not the same as in case 1. On the same day as the events of case 1 took place, but during the afternoon shift, this deputy had been engaged in shot firing in the same place, under the same conditions and with the same disregard of safety regulations. His eyes and chest were smarting, he felt unwell and had to sit down. Next day he was well and continued working. Three weeks later he began to spit up clots of blood and felt tired. He had a cough and complained of shortness of breath. On examination on May 10 his general condition appeared satisfactory, he was not dyspnœic. There were a few crepitations present at the left base, heart and blood pressure were normal, and a chest radiograph showed in both middle and lower zones a nodular type of density resembling the picture of pneumoconiosis (Fig. 3). No tubercle bacilli were found in his sputum. He was advised to rest and attended again on May 24. By then he was better and felt less breathless, the blood having disappeared from his sputum the previous week. There were still a few crepitations at the left base and radiographically the lung appeared much clearer (Fig. 4.). Because of the hæmoptysis the patient's doctor had him bronchoscoped and no abnormality was found. He resumed work in September and X-ray examination in November 1957 revealed further clearing of the lung; some reticulation was still shown, a finding not unusual in a miner of his age. On January 1, 1958, he was operated on for " duodenal ulcer," but cancer of the stomach was found and a gastrectomy performed. When last seen at the clinic on March 4, 1958, he had no respiratory symptoms and the radiographic picture of both lung fields had not changed. He died of cancer at his home in July 1958 and unfortunately it was not possible to obtain a post-mortem examination.

Discussion

Both these miners were engaged in shot firing and used as an explosive " Unigel " (Imperial Chemical Industries Ltd.). This is a gelignite type of explosive and contains, according to the manufacturer's label: (See table on following page)

In disregard of the " Explosive Regulations," which prescribe a shot firer should be at a distance of not less than 50 yards (45·7 metres) from the place of blasting and should wait five minutes before returning to the face, both men fired at a distance of 30 to 40 yards (27 to 37 metres) and returned immediately. They had never done this before, and moreover these particular blastings took place in a narrow space with poor ventilation. The " Explosive Regulations " aim at, and their observance succeeds in, avoiding harmful concentrations of " fumes from shot firing." These fumes " are usually composed of particles of finely divided solid matter, possibly with liquid droplets, accompanied by a

Ingredients	*Parts by weight*	
	Not more than	*Not less than*
Volatile matter	2·0	0·0
	Calculated on the dry explosive	
Nitroglycerine and nitroglycol ..	28·3	26·3
Mononitrotoluene	2·2	0·2
Nitrocellulose	1·4	0·4
Ammonium nitrate	32·5	29·5
Sodium chloride	30·3	28·3
Barytes	5·3	3·3
China clay	5·3	3·3
Oat husk meal	2·4	0·4
Diammonium phosphate	1·1	0·1
Acid magenta	0·1	0·001
A.S. No. 2 (optional)	0·01	0·001

mixture of gases, chiefly carbon dioxide and nitrogen, along with toxic gases, such as carbon monoxide, oxides of nitrogen, sulphuretted hydrogen, and ammonia. The particular matter will usually consist, in the main, of dust particles which, prior to the explosion, were lying on the floor, sides and roof in the vicinity of the shot hole, but particles formed by the disruption of the rock, and possibly particles of some of the constituents of the explosive charge, may also be present, along with droplets of nitrous or nitric acid" (Graham and Lawrence, 1948). The same authors and Lechner (1954) came to the conclusion that, with the use of "Permitted Explosives," carbon monoxide (CO) and hydrogen sulphide (H_2S), are very rarely present in harmful concentration in modern mines and their discussion may therefore be omitted. The harmful action of fumes from shot firing is attributable to the oxides of nitrogen, and nitrogen dioxide (NO_2), with its dimer nitrogen tetroxide (N_2O_4), is responsible for the irritant toxic action. Nitrogen oxide itself is non-irritant but reacts with oxygen to form nitrogen dioxide. In any one particular case it is difficult to ascertain how and how quickly this oxidation takes place in the gallery of a mine as well as within the respiratory tract, and "under a given condition these different gases and fumes are in equilibrium, but this may shift whenever the conditions are changed, which may explain in part the variations observed in the toxicological picture of poisoning from inhalation of nitrous fumes" (von Oettingen, 1941). These views are supported by Graham and Lawrence (1948). Tests of fumes from shot firing were carried out in a Northumbrian colliery during 1953 and 1954 (Gold *et al.*, 1955).

In normal long wall shot firing practice they have found up to 60 p.p.m. (per million parts of air) and in headings up to 133 p.p.m. of oxides of nitrogen. These figures appear high—in U.S.A. the "allowable limit" for oxides of nitrogen gases in mining operations is 25 p.p.m., but under normal working conditions the safety level is exceeded for a few seconds only because the fumes are rapidly diluted and dispersed by the ventilation current. In connection with the fatalities in Austrian mining

galleries experimental tests of fumes after shot firing by Lechner (1954) revealed a concentration of nitrogen dioxide as high as 80 p.p.m. which also decreased rapidly to below safety level.

Two of the fatal cases, recorded by this author, and who died of pulmonary œdema six and twenty hours after exposure, had gone through the fumes that had been carried towards them immediately after shot firing and therefore no time was left for the dilution of the gas. The third fatality was unusual as all precautions were observed, and out of a group of miners one man was taken ill three hours after the shot firing and died of pulmonary œdema seven hours later; none of the others had any symptoms. This striking case of individual susceptibility is, however, not unique and has long been known. Whilst massive exposure commonly leads to pulmonary œdema causing death in a great number of cases within a very short time McAdam's (1955) patient inhaled dense fumes, consisting mainly of nitrogen dioxide, which filled a laboratory after a group of flasks with red fuming nitric acid had exploded. In spite of this heavy exposure he had only a cough for twenty days, after which he became ill and died of bronchiolitis obliterans twenty-seven days after the accident.

Pulmonary œdema and bronchiolitis caused by the inhalation of nitrous fumes in grain silos have been observed in recent years in the U.S.A. and have been called by Lowrie and Schuman (1956) and by Delaney *et al.* (1956) " silofiller's disease." Peterson *et al.* (1949) found a concentration of 151 p.p.m. of nitrogen dioxide in a sample of air collected two days after silo filling. Apart from two fatal cases of pulmonary œdema the events in the cases of most of the affected farmers were essentially the same as in the cases of the two miners: a feeling of oppression and respiratory symptoms of varying degree immediately after exposure, thereafter either improvement or more or less stationary condition for two to three weeks, then marked deterioration with more or less severe respiratory symptoms (Grayson, 1956; Gailitis *et al.*, 1958). The majority developed bronchiolitis and in two of Lowrie and Schuman's cases the diagnosis was confirmed by autopsy. The radiographs of the American farmers and the Northumbrian miners showed in principle the same picture of nodular opacities differing only in degree. Those of the farmers who had steroid therapy responded dramatically—and the younger miner also responded immediately to Prednisolone, although it was given in a rather small dose. The older miner was less severely ill and recovered with rest alone. Both miners brought up clots of blood or bloodstained sputum—nothing of the kind was reported with the farmers. Both men failed to report the accident to the colliery management because they transgressed the regulations. This made it impossible to make any investigations in the colliery.

Conclusion

Two miners, a colliery deputy and a shot firer, under the pressure of work disregarded the " Explosive Regulations " during blasting operations and inhaled nitrous fumes which caused bronchiolitis. Men thus involved will be reluctant to give immediately and willingly a full history which would promote

early diagnosis and treatment, and both case reports illustrate this situation. The observance of the " Explosive Regulations " in collieries is essential, as shot firing is an intensive operation and no pressure of work should interfere with the standard of safety (H.M. Chief Inspector of Mines and Quarries, Report for 1957).

Summary

The cases of two miners who were exposed to fumes from shot firing are reported. Both suffered from bronchiolitis and recovered, the older man, however, died of cancer of the stomach fourteen months later. The problems of nitrous fumes poisoning in industry, particularly in mining, and the relevant literature are discussed.

My thanks are due to Mr. J. H. Gold, M.Sc.Tech., M.I.Min.E., Area Chief Scientist, No. 3 Area, Northern (N. & C.) Division, National Coal Board, for his advice and information on the technical problems.

REFERENCES

BECKLAKE, M. R., GOLDMAN, H. I., BOSMAN, A. R., and FREED, C. C. (1957): *Amer. Rev. Tuberc.*, **76,** 398.

DARKE, C. S., and WARRACK, A. J. N. (1958): *Thorax*, **13,** 327.

DELANEY, jun., L. T., SCHMIDT, H. W., and STROEBEL, C. F. (1956): *Proc. Mayo Clin.*, **31,** 189.

FRAENKEL, A. (1902): *Dtsch. Arch. klin. Med.*, **73,** 483.

GAILITIS, T., BURNS, L. E., and NALLY, T. B. (1958): *New Engl. J. Med.*, **258,** 543.

GOLD, J. H., HALL, F. W., and MCCORMICK, R. F. (1955): *Iron Coal Tr. Rev.*, **170,** 1087.

GRAHAM, J. I., and LAWRENCE, F. (1948): *Trans. Inst. Min. Engrs. Lond.*, **107,** 458.

GRAYSON, R. R. (1956): *Arch. intern. Med.*, **45,** 393.

LANGE, W. (1901): *Dtsch. Arch. Klin. Med.*, **70,** 342.

LECHNER (1954): " Sichere Arbeit," *Fachschrift für Sicherheitstechnik und Industrielle Medizin, Wien*, **3,** 1.

LOWRY, TH., and SCHUMAN, L. M. (1956): *J. Amer. med. Ass.*, **162,** 153.

MCADAMS, jun., A. J. (1955): *Amer. J. Med.*, **19,** 314.

MINES, Reports of H.M. Chief Inspector of Mines and Quarries, 1948-56 (Mines), 1957 (Mines and Quarries). London: H.M. Stationery Office.

NICHOLS, B. H. (1930): *Amer. J. Roentgenol.*, **23,** 516.

VON OETTINGEN, W. F. (1941): " The Toxicity and Potential Dangers of Nitrous Fumes." Division of Industrial Hygiene, National Institute of Health. Washington: United States Government Printing Office.

PETERSON, W. H., THOMA, R. W., and ANDERSON, R. F. (1949): Hoard's " Dairyman," 94, 870; quoted from Lowry, Th., and Schuman, L. M., *loc. cit.*

Brit. J. Dis. Chest (1959) **53**, 314.

SYNDROME OF ERYTHEMA NODOSUM, BILATERAL HILAR ENLARGEMENT AND POLYARTHRITIS

By K. Rajasuriya, N. Nagaratnam and M. Somasunderam

From the Department of Medicine, University of Ceylon

Erythema nodosum is a cutaneous manifestation—a non-specific tissue reaction to several invasive agents. Its occurrence denotes that the patient is specifically sensitive to the particular agent invading his blood stream, whether bacterial, viral, fungal or chemical in origin.

Erythema nodosum is one of the many manifestations of diseases like tuberculosis, sarcoidosis and rheumatic fever. Others, though rare, are chronic infective diseases such as lymphogranuloma inguinale, coccidiodes infections or leprosy. It occurs occasionally with chronic ulcerative colitis, appendicitis, cholecystitis, bronchiectasis, meningococcal septicæmia, dental infections, etc. (Johnson, Hanson and Good, 1951), and also as a sensitivity reaction to a number of drugs such as bromides, iodides and sulphonamides.

Its association with bilateral hilar adenopathy has been recorded by Kerley (1942), Middlemiss (1949), Sterling (1950), Crawley (1950), Johnson, Hanson and Good (1951), Dunner and Hermon (1952), Ellman (1956), Craig and Ferriman (1956), James, Thomson and Willcox (1956), James (1958), Citron (1958) and others.

The syndrome of erythema nodosum, bilateral hilar adenopathy and polyarthralgia is not uncommon: whether it is a disease *sui generis* or a manifestation of some other disease process, its ætiology remains uncertain. The onset is usually acute, with constitutional disturbances such as fever and malaise followed by polyarthralgia, erythema nodosum, leucocytosis and raised sedimentation rate. Radiological examination of the chest reveals a bilateral hilar enlargement, usually symmetrical and without involvement of the lung fields. There is no previous history of upper respiratory tract infection. The arthralgia and erythema nodosum disappear when the fever subsides. The hilar adenopathy usually lasts about eight weeks with a range of two to six months. The Mantoux reaction is negative or weakly positive.

It is the purpose of this paper to record two cases with a comment on their ætiology.

Case Report I

Male, aged 38, was admitted to the General Hospital, Colombo, with a history of fever of 11 days' duration, accompanied by a reddish eruption on his shins, tearing and discomfort of his left eye. The fever was sudden in onset and was accompanied by chills. The following day he had discomfort of his left eye with much tearing. Two days later he developed raised red patches on the dorsum of his feet, which later appeared on the shins and then on his arms and

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trunk. He had pain in his knee and elbow joints, but there was no swelling or effusion. He gave no history of a sore throat, cough, cold, discharge *per urethra*, hæmaturia, etc., nor of having taken any drugs. He had had no previous illness of note.

On examination the patient was febrile and his left conjunctiva was injected. The heart and lungs revealed no abnormality clinically. There were no palpable lymph glands. The liver was palpable one fingerbreadth below the right costal margin and the spleen one and a half fingerbreadths below the left costal margin. There were several raised erythematous patches, varying in size, on the dorsum of his feet, anterior aspect of both his legs, the forearms and back. On the forearm the patches were more crowded on the tattooed area.

Progress:

He was treated with Prednisolone (15 mgm. daily) and Penicillin. The fever settled after four days in hospital. The patient discharged himself the following day. The erythema nodosum had by then disappeared.

Investigations:

White cell count 10,400 per c.mm., D.C. Polymorphs 75%, Lymphocytes 24%, Eosinophils 1%, E.S.R. 122 mm. 1st hour, 126 mm. 2nd hour, Urinalysis —albumin nil, Deposits—pus cells 2-3 a field, and a few calcium oxalate crystals.

Readmission:

He sought readmission eight days later with the same complaint. He had developed a fresh crop of erythema nodosum two days after he left hospital, accompanied by fever and pain in his joints.

On examination he had conjunctivitis of his left eye, erythema nodosum on his arms and legs, some of recent origin, others healing. There was pitting œdema, tenderness and redness of the dorsum of both his feet. The heart and lungs revealed no abnormality. The liver was palpable one fingerbreadth below the right costal margin and the spleen one fingerbreadth below the left.

Progress:

He was treated again with Penicillin and Prednisolone. The fever, which was 101·6° F. on admission, settled down to normal the following day. He was afebrile for the rest of his stay in hospital. The erythema nodosum gradually disappeared and he was discharged eight days later.

Investigations:

Radiological examination of the chest revealed prominence of both hilar shadows. The rest of the lung parenchyma showed no abnormality (Fig. 1)*. X-ray of his hands showed no cystic changes of sarcoidosis. White cell count 7,200/c.mm., D.C. Polymorphs 64%, Lymphocytes 34%, Monocytes 1%, Eosinophils 1%. Serum Calcium 9·7 mg. %, Brucella agglutination test—*Br. mellitensis* 1 : 20, *Br. abortus* 1 : 10. Bleeding Time—1½ mins., Clotting Time 5 mins. Total Proteins: 5·7 g. %, A/G ratio 0·7, Electrophoretic pattern: alb. 33·2%, alpha 1/7·7%, alpha 2/12·9%, beta/15·4% and gamma/30·8%, serum bilirubin: Total 0·5 mg. %, direct 0·2%, indirect 0·3%, cephalin cholesterol 1+, Kunkel's test 16 units, serum transaminase (S.G.O.T.)

* The figure numbers in the text refer to Plates XLVI-XLVII.

10 units, Blood Group: IV o, and Rh negative. Mantoux negative (1 : 10,000). On the sixth day, following the intradermal test, the site of injection was raised, red and about 5 cm. in diameter. A liver biopsy specimen showed persistence of normal architecture. There was no fibrosis in the portal tracts, but there were aggregates of lymphocytes both in the portal tracts and in the liver parenchyma, and there appeared to be a mild lymphocytic infiltration in the sinusoids as well. There was no necrosis, nor were there any epithelioid follicles characteristic of sarcoidosis, nor was there any evidence of tuberculosis (Fig. 2 *a*, *b*, *c*). A biopsy of skin was done from the tattooed area on his forearm, and showed non-specific changes. The epidermis was somewhat thinned, and there were collections of round cells in the deeper layers.

Further progress:

He reported to the out-patients' clinic two months later. He had no symptoms. Radiological examination of his chest showed somewhat asymmetrical enlargement of the hilar regions, the left more than the right, with some involvement of the lung parenchyma.

Case Report II

Female, aged 35, was admitted with a history of fever of two weeks' duration. The fever was accompanied by chills and frontal headache. She gave no history of a sore throat, cough, cold or urinary symptoms.

On examination the patient was febrile. The heart and lungs revealed no abnormality. The spleen was just palpable. A diagnosis of typhoid fever was made and she was treated with chloramphenicol.

Progress:

On the fourth hospital day she developed conjunctivitis of her left eye. The fever settled on the fourth day of admission but rose again two days later, accompanied by erythema nodosum on her legs. She complained of flitting joint pains. Her fever gradually settled with disappearance of conjunctivitis and erythema nodosum and she was treated with streptomycin. She was discharged from hospital three weeks later.

Investigations:

X-ray of her chest on admission revealed bilateral hilar prominence, but the lung fields were normal. W.B.C. 3,600/c.mm., Lymphocytes 39%, Monocytes 3%. The Standard Agglutination Test (Widal) and Weil-Felix reaction were negative. Sedimentation rate: 105 mm. 1st hour, 116 mm. 2nd hour. Blood group: Rh positive.

Further progress:

Three months later X-ray showed a much greater prominence of the hilar shadows. Sedimentation rate: 38 mm. 1st hour, 86 mm. 2nd hour. She had no symptoms.

Comment:

Kveim's test was not done in either case as the antigen was not available.

PLATE XLVI

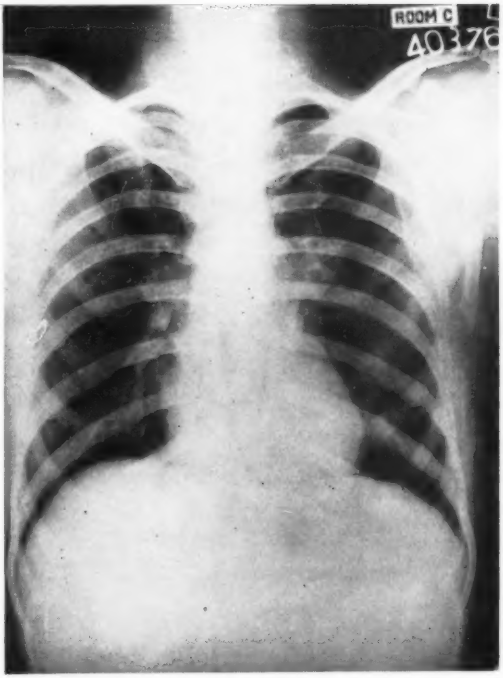

FIG. 1.—Radiogram of chest showing prominence of hilar shadows. (Case 1.)

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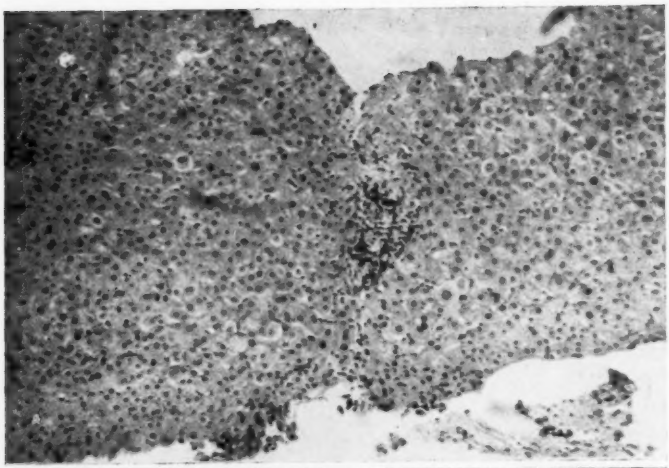
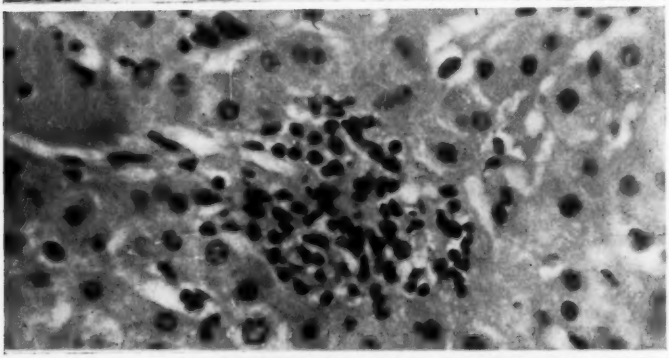
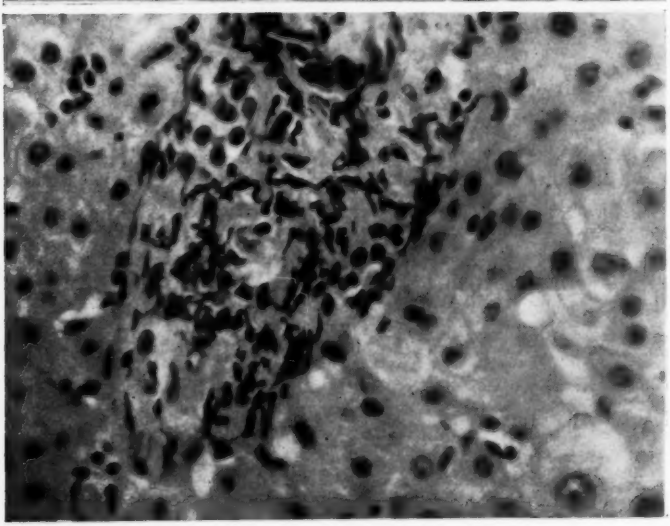


A. Aggregates of lymphocytes both in the portal tracts and in the liver parenchyma, Haematoxylin and Eosin. ×150.



B. High power of one of the aggregates, H. and E., ×600.



C. Same, showing lymphocytes and fibroblasts, H. and E., ×600.

FIG. 2.—Histological appearances in the liver.

Discussion

The clinical picture of this syndrome has been adequately reviewed and described in previous reports. Both our cases exhibited most of the classical symptoms and signs: viz. fever of sudden onset, erythema nodosum, bilateral hilar adenopathy and joint involvement.

The clinical features of this syndrome individually and in different combinations are common manifestations of tuberculous infection and of sarcoidosis. Hence these two conditions have to be seriously considered in the ætiology of this syndrome. In primary tuberculosis the glandular element of the primary complex is unilateral; except in the negroes, who may develop massive bilateral hilar gland enlargement with primary tuberculosis (Anderson, 1956). Both our cases had conjunctivitis, but not of the phlyctinular type, which is associated with primary tuberculosis. In tuberculosis the Mantoux reaction is nearly always positive. Gamstedt (as quoted by Johnson *et al.*, 1951) has observed a high percentage of patients exhibiting a negative tuberculin reaction prior to development of erythema nodosum, but a positive one develops at the time of appearance of the cutaneous lesions or shortly thereafter. It is now generally accepted that sensitivity to tuberculin is very high during the eruption of erythema nodosum, when the latter is associated with tuberculosis.

According to James (1958), Mitchell-Higgs and Feiwel (1958), Citron (1958) and others the combination of arthralgia, erythema nodosum and bilateral hilar adenopathy in young adults, particularly women, is a common manifestation of early sarcoidosis. Both cases illustrate several manifestations in favour of early sarcoidosis. In addition to the erythema nodosum, bilateral hilar enlargement, the occurrence of eye lesions and the negative Mantoux are in favour of sarcoidosis. In Case 1 another interesting feature is the Rh negative blood group. Cudcwicz (as quoted by Anderson, 1956), found that an unusually large proportion of patients who had sarcoidosis, had an Rh negative blood group. There is certainly a constitutional factor in the interesting and unsolved problem of sarcoidosis. In Case 1 there were several patches of erythema nodosum centred in the area of tattoo on the patient's forearm. Anderson (1956) quotes a number of instances where either recent trauma with entry of foreign material into the skin, or an inoculation, vaccination or a surgical incision in the past, had given rise to skin lesions typical of sarcoid. The biopsy of the skin in Case 1 showed no specific lesion, though time only can tell whether or not the typical lesion of sarcoid will develop.

The liver in Case 1 did not show the typical follicles of a sarcoid lesion. Mather, Dawson and Hoyle (1955) drew attention to 4 cases known to have had sarcoidosis where no follicles were found, but had lymphocytic aggregates in the portal tracts (similar to the findings in Case 1). They, in a study of the evolution of the hepatic follicle, did repeated biopsies in 10 patients. In 2 they were repeatedly normal in spite of typical clinical and radiological features of sarcoidosis; in 3, unchanged for four years, though the pulmonary disease remained. Two cases showed spontaneous resolution. In another 2, the follicles were several times larger and in 1 the follicles were fewer and smaller, and contained a predominance of lymphocytes and fibroblasts twelve months

after the original biopsy. Hepatic granulomatous lesions having a common histological pattern, but sometimes differing in minute detail, occur in a number of diseases of which, according to Sherlock (1955), sarcoidosis, tuberculosis and brucellosis are the commonest, though they may be found in chronic beryllium poisoning, erythema nodosum, syphilis, leprosy and mycotic infections. The interpretation of these findings can be difficult at times.

Against an ætiology of sarcoidosis is the relatively short duration of the illness as compared with sarcoidosis, which is regarded as a chronic illness. Craig and Ferriman (1956) report 5 cases in whom recovery had been maintained for from 2 to 5 years. According to them, if sarcoid changes were demonstrated in such cases it would be necessary to postulate an acute completely recoverable form of Boeck's sarcoidosis, or another agent capable of causing such changes.

Rheumatic fever may at times give rise to some difficulty in the early stages, especially if the joint pains together with fever precede the erythema nodosum. However, the subsequent course makes it obvious, for in this syndrome the skin lesions and bilateral hilar adenopathy soon appear and there is no cardiac involvement. Erythema nodosum associated with streptococcal infection is usually preceded by upper respiratory infection, and the anti-streptolysin O titre is raised. The chest X-ray is normal. Sulphonamides, especially sulphathiazole, give rise to similar skin manifestations, and this tends to recur if the drug is given again. When associated with lymphogranuloma inguinale other signs of the disease make the diagnosis obvious. Erythema nodosum is one form of lepra reaction, and occurs during treatment with sulphones. In coccidiodes infections the cutaneous manifestations are late.

In conclusion, sarcoidosis appears to be the most likely cause of this syndrome although only a long-term follow-up of these patients will provide confirmatory evidence.

Summary

Two cases of the syndrome are described, and their ætiology is discussed.

We wish to thank Dr. W. D. Ratnavale for use of the histological slides.

REFERENCES

ANDERSON, H. J. (1956): *Practitioner*, **177**, 160.
CITRON, K. M. (1958): *Postgrad. med. J.*, **34**, 268.
CRAIG, M. M., and FERRIMAN, D. G. (1956): *Proc. roy. Soc. Med.*, **46**, 867.
CRAWLEY, F. E. (1950): *Brit. med. J.*, **2**, 1362.
DUNNER, L., and HERMON, R. (1952): *Brit. med. J.*, **2**, 1078.
ELLMAN, P. (1956): In Daley and Miller, " Progress in Clinical Medicine." London: J. and A. Churchill.
GAMSTEDT, quoted by Johnson *et al.* 1951.
JAMES, D. G. (1958): *Postgrad. med. J.*, **34**, 240.
JAMES, D. G., THOMSON, A. D., and WILLCOX, A. (1956): *Lancet*, **2**, 218.
JOHNSON, C. C., HANSON, N. O., and GOOD, G. A. (1951): *Ann. intern. Med.*, **34**, 983.
KERLEY, P. (1942): *Brit. J. Radiol.*, **15**, 155.
MATHER, G., DAWSON, J., and HOYLE, C. (1955): *Quart. J. Med.*, **96**, 331.
MIDDLEMISS, J. H. (1949): *Brit. J. Radiol.*, **22**, 375.
MITCHELL-HIGGS, G. B., and FEIWEL, M. (1958): *Postgrad. med. J.*, **34**, 274.
SHERLOCK, S. (1955): " Diseases of the Liver and Biliary Tract." Oxford: Blackwell.
STERLING, K. (1950): *Amer. Rev. Tuberc.*, **62**, 112.

Brit. J. Dis. Chest (1959) **53**, 319.

BRONCHOGRAPHY IN PULMONARY TUBERCULOSIS

By T. F. McCarthy and D. P. Misra

From the Stockport Clinical Area

Since modern chemotherapy of tuberculosis has minimised the risk of spread of disease after bronchography and newer contrast media no longer obscure the radiological appearances, it was decided to carry out bilateral bronchography on a series of tuberculous patients in sanatorium. The purpose was to decide the place of the procedure in assessing treatment and prognosis and to correlate the radiological and bronchographic appearances with the pathological findings in the resected specimens. The method used was to introduce propyliodone "Dionosil" via the crico-thyroid membrane under local anæsthesia. No case of spread of disease was encountered and there were no significant complications of the method, although a mild febrile reaction lasting three to four days occurred quite commonly.

Analysis of Material

Age and Sex Distribution

In the series of 114 patients, the age and sex distribution is as shown in the accompanying table, the ages of the majority of the patients falling between 20 and 50 years.

Table 1

Age	10-19	20-29	30-39	40-49	50-59	60 +
Male	7	13	16	17	5	1
Female	10	21	13	9	2	nil
Total	17	34	29	26	7	1

Distribution of Bronchiectasis

A total of 37 patients, 21 male and 16 female, had normal bronchograms. The remaining 77, 38 males and 39 females, manifested varying degrees of bronchiectasis. The segmental distribution of the bronchiectasis is as shown in Table 2.

The distribution of bronchiectasis thus closely follows the parenchymal involvement of the disease, the apical and posterior segments of the upper lobe being most commonly involved. In the lower lobes the apical segment was most frequently involved when disease affected one segment. When the basal segments were affected, apical segment involvement was a frequent accompaniment.

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TABLE 2

Right lung		*Left lung*	
Upper lobe (all segments involved) ..	15	Upper lobe (all segments involved)	15
Apical segment	13	Apical posterior segment	24
Posterior segment	14	Anterior segment	6
Anterior segment	4	Lingula	5
Middle lobe	5		
Lower lobe (all segments involved) ..	4	Lower lobe (all segments involved)	8
Apical segment only	5	Apical segment	8
		Anterior basal segment	1
		Lateral basal segment	1

Correlation between Radiological and Bronchogenic Findings

Correlation between the radiological extent of disease and the bronchographic findings is shown in Table 3. The disease in each lung field has been separately classified as minimal when it did not involve more than one interspace, or extensive when more than two zones were heavily infiltrated, grossly fibrosed or cavitated. Intermediate disease was classified as moderate.

TABLE 3 (LUNGS CLASSIFIED SEPARATELY)

Radiological findings		*Bronchographic findings Degree of bronchiectasis*			
Extent of disease	*No. of cases*	*Nil*	*Slight*	*Moderate*	*Severe*
No lesion	41	41	nil	nil	nil
Minimal	51	50	1	nil	nil
Moderate	120	42	34	38	6
Extensive	13	nil	nil	nil	13
Thoracoplasty	3	nil	nil	3	nil

The correlation between the extent of disease and the degree of bronchiectasis was close, except in disease of moderate severity.

Extensive disease was in every case accompanied by severe bronchiectasis. Minimal disease showed a normal bronchogram in every case except one, where mild bronchiectasis of a small bronchus was demonstrated. No bronchiectasis was seen in a lung field judged to be normal radiologically. With moderate disease various degrees of bronchiectasis were seen and in forty-two instances a normal bronchogram was found. Six cases of moderate disease showed severe bronchiectasis. No case of stenosis of a main bronchus was found in this series.

Bronchial Disease in Resection Specimens

Among the 114 patients 27 had resections carried out and in 2 the resections

were bilateral. In nineteen of the twenty-nine resection specimens bronchial dilatation was found. In each case bronchiectasis had previously been demonstrated by bronchography. The remaining 10 had normal bronchograms and no bronchial dilatation was seen in the specimens. There was thus no discrepancy between bronchographic and pathological findings in our cases.

The resected specimens showed evidence of active tuberculosis in twenty-three instances and no evidence of remaining tuberculous activity was found in six. In two, both pneumonectomy specimens, histological appearances of tuberculosis were found in the bronchial walls, but no evidence of tuberculosis was found in the bronchi of the remainder. One of the cases of tuberculous bronchitis had organisms resistant to streptomycin, PAS and isoniazid; in the other, sputum conversion had occurred prior to operation, after ten months of continuous chemotherapy with all three drugs. In this case resistant organisms had never been demonstrated.

Discussion

The predilection of tuberculosis for the posterior and apical segments of the upper lobe and the apical segments of the lower lobe is well known. From the analysis it is evident that bronchiectasis in tuberculosis was most commonly encountered in those segments which also frequently showed bronchial crowding due to collapse and fibrosis.

The classification of the extent of disease was based on the amount of lung tissue involved and not on the character of the lesion. As previously stated, extensive parenchymal disease was accompanied by gross bronchiectasis and minimal disease by normal bronchograms. The greater variation of the degree of bronchiectasis in disease classified as moderate was probably explained by the duration of the tuberculous process. This is difficult to estimate since, as some of the patients in the moderate groups were discovered by mass radiography, they at least must have passed through a comparatively symptom-free stage. That some of the disease in this group was of long duration is suggested by the presence of calcification in the lesions.

Bronchiectasis was found on bronchography in 68 per cent. of cases in this series. In a series of sanatorium patients McLeod (1958) found bronchiectasis in 78 per cent. and Buckles *et al.* (1951) found bronchiectasis suggested in 115 of a group of 222 patients studied (52 per cent.). In their series, however, suspected pre-operative and proved post-operative bronchiectasis did not parallel one another in frequency. In the present series no such discrepancy was noted.

Enlarged tuberculous glands in the hilar regions produce lobar collapse in childhood and the importance of this in bronchiectasis of the middle lobe was stressed by Brock (1950). Lee Lander (1938) considered that tuberculous tracheo-bronchitis sometimes produces obstruction, either of a main bronchus leading to massive atelectasis, or of a primary (lobar) bronchus leading to lobular atelectasis. His explanation of the frequency with which bronchiectasis complicates tuberculous conditions of the lung and the manner in which smaller divisions of the bronchi are involved is that secretions sucked down the

bronchus produce obstruction of the terminal bronchioles causing lobar collapse. The increased pull upon air-containing bronchi dilates them, as their walls still contain elastic tissue capable of normal functions. The tuberculous secretions then cause infection rendering the bronchiectasis permanent. Lee Lander stated that in his opinion fibrosis of the lung played no part in the production of bronchiectasis, as bronchograms carried out in cases of silicosis demonstrated normal bronchi in the majority of cases.

Medlar (1955), in a study of pathological specimens, noted that the majority of the tuberculous lesions were parenchymal and were distributed in the same manner in bronchiectatic and non-bronchiectatic lungs. It seemed unlikely to him that the bronchiectasis could be related ætiologically either to tuberculous or non-tuberculous infection, but that once such abnormal bronchi became infected, the production of necrotic endobronchial lesions made tuberculous infection the more difficult to heal. His specimens showed the presence of necrotic endobronchial tuberculosis in some of the cystic bronchiectasis seen and also non-tuberculous infection in other parts of the specimen. He thus believes that bronchiectasis coexists with tuberculosis and that tuberculous ulceration of some of the bronchial cysts may subsequently occur. He stated that the organisation of non-necrotic tuberculous pneumonias may cause extensive parenchymal scarring leading to distortion of the normal bronchial pattern. These bronchi may be enlarged and tortuous but still possess a normal structure, as may the distorted bronchi under prolonged pneumothorax or thoracoplasty.

The mechanism of the production of bronchiectasis has been explained by several theories. First, the condition may be induced by an obstruction within or without the bronchi or bronchioles, with collapse in the lung and a suppurative bronchial disease, either proximal or distal to the obstruction. Second, an episode of necrotising bronchitis may destroy the structure of the bronchial wall. The third concept considers that bronchiectasis is caused by traction exerted by parenchymal fibrosis.

While tuberculosis can coexist with non-tuberculous bronchiectasis, theories of causation of bronchiectasis in tuberculosis must take into account its close association with the tuberculous lesion, which in our view constitutes the major factor in the cause of bronchiectasis. The tuberculous infection may be either in the bronchi, with obstruction of the lumen and collapse in the lung, or destruction of the bronchial walls, or it may be in the parenchyma with collapse and fibrosis.

Most cases had over six months' chemotherapy prior to bronchography and all at least three months. Prior to surgery all cases had over six months' chemotherapy. The satisfactory response of tuberculous bronchitis to chemotherapy is demonstrated by the fact that in only two resection specimens was active tuberculosis demonstrated in the bronchial walls. In one of these cases the organisms had been found pre-operatively to be resistant to all the chemotherapeutic agents used.

Thus whether bronchiectasis is dependent on tuberculous endobronchial disease or on the parenchymal lesion, prolonged chemotherapy of cases with

early lesions, prior to the advent of bronchiectasis, should materially reduce its incidence in future.

Routine bilateral bronchography as carried out in this series has helped to understand the pathology of bronchiectasis in pulmonary tuberculosis. However, since the place of surgery in pulmonary tuberculosis has become smaller and more accurately defined and since greater reliance is being placed on long-term chemotherapy, in which bronchography is of little value in the assessment of prognosis, we feel from our own experience and from other published series that routine bronchography in all cases is no longer indicated. Certain indications, however, remain for its use. Prior to surgery bronchography will demonstrate the association between the parenchymal disease and the bronchi, and by excluding bronchiectasis unsuspected by radiography or tomography, assist in the decision as to the type and extent of the surgery. It may show bronchiectasis when hæmoptysis occurs in seemingly inactive disease, or when apparent control of the tuberculous parenchymal disease has been obtained and when symptoms, especially cough and sputum, persist in spite of chemotherapy.

Summary

A description is given of an unselected series of sanatorium patients with active pulmonary tuberculosis, who had bilateral bronchography carried out.

The radiological and bronchographic findings have been correlated and compared with the pathological appearances in resection specimens.

Theories of the mechanism by which bronchiectasis is produced in pulmonary tuberculosis, the value of bronchography in the assessment of cases and the indications remaining for its use, are discussed.

REFERENCES

Brock, R. C. (1950): *Thorax*, **5**, 5.
Brock, R. C., Conn, R. J., and Dickinson, J. R. (1937): *Guy's Hosp. Rep.*, **87**, 295.
Buckles, M. G., *et al.* (1951): *Amer. Rev. Tuberc.*, **64**, 4, 394.
Buckles, M. G., and Neptune, W. G. (1950): *Ibid.*, **61**, 2, 185.
Clegg, J. W. (1953): *Thorax*, **8**, 3, 167.
Lee Lander, F. P., and Davidson, M. (1938): *Brit. J. Radiol.*, **11**, 65.
(1938): *Brit. med. J.*, **1**, 1047.
McLeod, J. A. (1958): *Brit. J. Tuberc. and Dis. Chest*, **52**, 3, 225.
Medlar, E. M. (1955): *Amer. Rev. Tuberc.*, **3**, 2, 1.

Brit. J. Dis. Chest (1959) **53**, 324.

REVIEWS OF BOOKS

Treatment of Lung Cavities and Endobronchial Tuberculosis. By BERYL E. BARSBY. Edinburgh: Livingstone. Pp. 147. Illus. 20s.

This interesting book serves to remind us of the serious problem tuberculosis still presents in tropical countries. In Malaya, with its mixed population, crowded living accommodation and low standard of living and education, the infection rate is high both in urban and rural districts. Facilities for treatment are very limited except in the few large towns and difficulties of follow-up and out-patient supervision almost insurmountable. Nevertheless, a careful study has been made of the incidence and significance of endobronchial disease. 1,126 bronchoscopies were performed and the bronchoscopic appearances correlated with biopsy examination. Six grades of endobronchitis are defined, the earliest being redness and œdema of an intact mucosa. General anæsthesia is recommended, as the earlier changes may well be overlooked if the examination is performed under local. Examination of 100 untreated cases selected at random revealed 75 with endobronchial disease but no correlation between the stage of endobronchitis and radiological type of disease.

The symptoms and signs of endobronchitis are discussed and evidence is adduced that pooling of sputum and direct implantation is a common mode of spread. The most effective drug treatment was daily streptomycin and Isoniazid continued until both bronchial and parenchymal lesions are apparently healed, 65 per cent. of bronchial lesions being completely healed within seven months.

The author's views on the management of cavities, medical collapse therapy and surgical treatment are clearly outlined and supported by clinical results. Modified postural retention combined with orthodox chemotherapy has proved of great value in achieving cavity closure, while collapse therapy is only used to maintain cavity closure and permit an earlier discharge from hospital. Because of the shortage of beds only cases with cavitated, acute or advanced bilateral disease can at present be admitted to hospital, but good results are claimed for out-patient chemotherapy in patients with active infiltration.

The author is to be congratulated on a careful piece of clinical research and the results of its practical application under the difficult circumstances peculiar to Malaya.

F. H. SCADDING.

Aktuelle Probleme der Kindertuberkulose. By H. WISSLER. Stuttgart: George Thieme. Pp. 71. DM.12.80.

This monograph deals with some of the present-day problems encountered in childhood tuberculosis. Many of the questions discussed in this book were raised not very long ago at two international conferences, namely " Seminaire sur le Traitment de la Tuberculose de l'Enfant," Paris, 1955, and the " Symposium on Tuberculosis in Infancy and Childhood," November 1955, at Denver.

The importance of INAH-resistant bacteria is discussed. The question as to whether the anti-tuberculous drugs should be administered in cases of primary tuberculosis is answered on the whole in the affirmative, for there is now substantial evidence that the antibiotics reduce the incidence of complications such as meningitis, etc., especially in infants. The role of cortico-steroids

in the treatment of tuberculous meningitis is fully reviewed. The policy to be adopted with regard to B.C.G. immunisation is also dealt with. On the other hand, the place of surgery in the treatment of primary tuberculosis seems not yet clearly defined. The section dealing with bone and joint tuberculosis, short though it is, could have been left out with advantage.

On the whole this little book gives a very good survey of the problems of tuberculosis in childhood, although many of them still remain unresolved.

H. C. NOHL.

Recent Advances in Respiratory Tuberculosis. By FREDERICK HEAF and N. LLOYD RUSBY. London: Churchill. Pp. 284. Illus. 35s.

It is now ten years since the last edition of this book and the amazing advances of this period, especially in relation to chemotherapy, have made this fifth edition overdue.

The remarkable decline in the mortality rate of respiratory tuberculosis has not been matched by a comparable decline in morbidity, and complacency must, therefore, be avoided. Moreover unrestricted air travel, annihilating distance, can all too readily bring to this island the problems of tuberculosis that still affect backward countries. Nevertheless the changes of the last decade have demanded a complete reappraisal of the whole problem of respiratory tuberculosis. The fifth edition reflects this change in attitude and is to be cordially welcomed.

Modern problems in relation to epidemiology, prevention, studies in respiratory function, chemotherapy, surgical methods, prognosis, etc., are all admirably reviewed. The chapter on some miscellaneous advances is timely, and current problems of tuberculosis and pregnancy, tuberculosis and diabetes, tuberculosis and carcinoma, tuberculosis and sarcoidosis, and tuberculosis and peptic ulceration, are considered in the light of modern advances.

There is also a useful chapter on developments in chest radiography and radiation hazards. Miniature chest radiography is discussed in relation to factors such as " observer error " and its reduction, large-scale surveys and, future use of M.M.R. units. There are also useful chapters on collapse therapy and treatment by resection. The diminished use of collapse therapy, both medical and surgical, indicates the comparatively small part these procedures will play in the future.

All in all the volume can be strongly recommended as an up-to-date and well-balanced contribution by two writers, experts in this field.

PHILIP ELLMAN.

Advances in Tuberculosis Research/Fortschritte der Tuberkuloseforschung/Progrès de l'Exploration de la Tuberculose. Vol. 9. Edited by HANS BIRKHAUSER, HUBERT BLACH and G. CANETTI. Basle/New York: S. Karger. Pp. 342. Illus. S.Fr.64.

The latest volume of this series comprises authoritative papers by authors of various nationalities and includes an American review of the recent history of tuberculosis, an interesting Japanese study on the production of experimental tuberculous cavities in rabbit lungs, a Russian description of the histological changes in the nervous system of sufferers from various forms of tuberculosis. There are also a Scandinavian study of the relationship of sarcoidosis and

atypical tuberculosis, a German study of experimental methods of testing anti-tuberculous drugs in the mouse, a French account of enzyme changes associated with isoniazid-resistant tubercle bacilli, and a Canadian exposition of the uses of radioactive isotopes in the study of experimental tuberculosis.

In general the work is of a high standard and its value is enhanced by an extensive bibliography. The Russian work is in ponderous English and tends to be obscure, faults due probably to the translation. The major criticism relates to editorial inconsistency; for example, the references are done in widely different ways. No rules of bacterial nomenclature are followed (*Esch. coli* and *E. coli* occur in the same paper), units of measurement are not standardised (g. microgram, mcg.), and the tables do not always give the information promised. Slipshod editing of this kind can only cast doubt on the validity of the material being reported.

R. E. M. THOMPSON.

Handbook of Respiration. National Academy of Sciences. National Research Council. Philadelphia and London: W. B. Saunders. Pp. 403. $7.50.

This remarkable book is a directory in tabular form of the more important measurements which have been made in the study of respiration in man, in animals and in vegetables. Information is clearly related to its source: the book therefore includes what must be the best collection of references on the subject. In each section man and other animals are considered together. This presentation of the comparative physiology of respiration greatly increases the value of the work.

Subjects presented include basic physical and chemical data, anatomical measurements, pulmonary function measurements, respiratory characteristics of blood, its erythrocytes and pigments, mechanics of breathing, artificial respiration, effects of exercise, effects of drugs and inhaled gases, and tissue respiration of animals and plants. The clarity and brevity with which such a wide range of information is presented is a minor miracle of editorial staff work.

The annotations, graphs and line charts on the subjects of blood oxygen dissociation and acid-base balance and imbalance both present the information and show how and where it may be used in practice. The section on artificial ventilation includes Radford's nomogram of tidal volumes required for different breathing frequencies in people of different weight and a tabulated discussion of the use, advantages and disadvantages of different respirators and techniques of artificial respiration.

Though there is a great deal of information of practical and theoretical value to the clinician the greater part of the book is more academic. This part may not be without interest to the practical man. As he turns the pages he may learn, for example, that a horse breathes as much as 100 litres a minute at rest and a mouse only 23 c.c. (Respiratory Rate, Tidal and Minute Volumes: Vertebrates), that bicycling at ten miles an hour on the level requires about the same oxygen consumption as walking on the level (Energy Cost of Progression: Man), and that a llama in the high mountains has an oxygen dissociation curve well to the left of the domestic animals of the plains (Blood O_2 dissociation curves: Mammals). One wonders if the llamas at the zoo still have this distinction.

L. H. CAPEL.

Die Entwicklung der Tuberkulosebehandlung seit 100 Jahren. By G. DOMAGK, L. HEILMEYER, and H. KRAUSS. Stuttgart: George Thieme. Pp. 47. DM.12.

Short papers by three well-known experts paint an interesting picture of the development which the treatment of tuberculosis has undergone. They begin with the creation of the first sanatorium by Brehmer in 1854 at a time when Koch's bacillus was not yet known. The discovery of Koch opened a second phase in the fight against the disease, and the papers finally deal with chemotherapy and surgical treatment. All in all these discourses present felicitously some chapters in the history of tuberculosis.

Neue Tuberkulosestatica und Tuberkulosestatica-Resistenz in Tuberkelbakterien. Symposium, February 1958 in Freiburg i. Br. Edited by A. M. WALTER. Stuttgart: George Thieme. Pp. 152. DM.19.80.

A symposium uniting clinicians, bacteriologists and experimental biologists in a discussion on recent advances in the chemotherapy of tuberculosis is bound to be of great interest to chest physicians. Experts from various countries contributed to the discussions and there was a wide variety of subject matter and opinion. While no definite result could be reached it was recognised that effective chemotherapy of tuberculosis may at times present difficulties, especially with regard to drug resistance which may be a problem in the treatment of tuberculous patients.

This small book will be indispensable to every specialist dealing with chest diseases.

Roentgenanalyse der Neugeborenen-und Saeugerierlunge. By ZOLTAN ZSEBOEK. Stuttgart: Georg Thieme. Pp. 160. Illus. DM.75.

This book describes modern methods for dealing with an important subject. The research that has been carried out in relation to radiological anatomy exemplified in the radiograms is infinitely painstaking. Casts have been made, macroscopic methods used, and as a result it has been possible accurately to confirm, amplify or even contradict previous results.

The author puts forward his own views dogmatically and, partly for this very reason, these cannot always be taken as the final word on any subject. This is especially true of the chapters on the hilum and the thymus. The use made of relevant literature is likewise open to criticism. Apart from this, a book that deals so profoundly with the anatomical basis of skiagrams merits the attention and acclaim of clinicians and radiologists.

S. ENGEL.

Funktionelle Roentgendiagnostik des Mediastinums am Beispiel des Bronchial-karzinoms Demonstriert. By R. KRAUS. Stuttgart: Georg Thieme. Pp. 55. 33 Illustrations.

This is a short monograph in which the author assesses kymography in the study of the œsophagus in relation to secondary mediastinal deposits associated with primary bronchial carcinoma. The first chapter contains a review of kymography and other radiological methods used in the diagnosis of mediastinal metastases. In the following chapters the more specific problems are dealt with. The author is able to demonstrate how certain changes in the œsophageal kymogram correlated well with adjacent mediastinal metastatic deposits.

The same applies to an experimental study where the nerve supply to the œsophagus is paralysed by local anæsthetic. This produces alterations in the kymogram which are very similar to those seen in metastases destroying the nerve fibres in the mediastinum. There is finally a suggestion put forward that the neuropathy associated with carcinoma of the bronchus may be partly due to metastatic lesions in mediastinal nerve fibres and ganglia. Dr. Kraus has produced an interesting monograph: a considered experimental study which is well produced and documented.

R. E. STEINER.

Acta Tuberculosea Scandinavica. Supplement XLII (42). BAUER, HANNS J.: The Observer Error in Multiple Interpretation of Photofluorograms. Copenhagen: Ejnar Munksgaard. 1958.

This investigation is in two parts. Firstly, there is an inquiry into the discrepancies between fourteen physicians who corrected each other's readings in the general material of the Mass Radiography Centre of the Royal Medical Board in Sweden. This material consisted of 2,084,583 photofluorograms taken between 1953 and 1956. The results of the general investigation showed that 59,708 cases were diagnosed on the first reading and 63,852 on the second reading. After adjustments for over reading, it was found that 8·3 per cent. of the truly positive cases were not found until the second reading. Between the readers under-diagnosis varied between 2·9 and 27·8 per cent. of the final numbers requiring follow up. Over reading, on the other hand, varied between 0 and 10·9 per cent.

Secondly, there was within the general inquiry a special test in which 3,268 photofluorograms were arranged to contain 99 selected abnormal cases for whom therapeutic action was considered necessary. Readers did not know how many selected abnormals were thus hidden in the material, nor that these pictures were occurring on an average once for every 30 films read. This test material was read by eight physicians and re-read one to two months later. The results of the second investigation showed that on single reading the readers correctly diagnosed between 27 and 81 of the 99 test cases. The average diagnosed was 61 per cent. and the average missed 39 per cent. Even some far advanced cases were missed by some readers. Double reading gave consistently better results and 76 per cent. were correctly diagnosed. Double reading by the various possible pairs of readers were analysed.

The whole work is a very detailed study which anyone interested in observer variability in X-ray reading will wish to examine closely. In general, the enormous advantage of double reading over single reading is fully demonstrated.

CHRISTOPHER CLAYSON.

Grundriss der Perkussion und Auskultation. By G. LANDES and — BODECHTEL. Berlin: Walter de Gruyter. Pp. 131. DM.9.80.

This little book, called the "fundamentals" (Grundriss) of percussion and auscultation, tries to get to the root of the matter. Thus a lengthy description of the physical properties of percussion waves in terms of Hertzian waves, or a 3-page mathematical discussion on the module of elasticity of the arterial system may be regarded by some as getting down to the very foundations of the subject, but would be considered in this country as carrying theory or, for that matter, thoroughness a bit too far.

A book which discusses in great detail how to percuss the borders of the heart and measure the band of resonance in the supraclavicular regions (Kronig's " Isthmus ") strikes one as out of touch with reality. I am sorry for the medical student who is still expected to learn all the old signs, *e.g.* Grocco's triangle (*Rauchfuss'sches Dreieck, signe du sou*, etc.).

Handbuch der Tuberkulose. In five volumes. Edited by J. HEIN, H. KLEINSCHMIDT and E. UEKLINGER. Stuttgart: George Thieme, Vol. 1. Pp. 832. DM.178.

This book, the first of a five volume series, is a veritable encyclopædia of tuberculosis. It deals with the history of the disease, the bacteriology, immunology, allergy and the tuberculin reactions. Serodiagnosis, epidemiology and many other aspects of tuberculosis are also fully discussed. The great progress made over the past twenty years in relation to many aspects is described.

The list of contributors, all experts in their special subjects, is international. Thus the section on the morphology and metabolism of the tubercle bacillus is written by Suter and Bloch of the U.S.A., while another section on the sources and dissemination of tuberculosis is contributed by E. Hedvall from Uppsala, Sweden. This international representation assures the place of the book as a major work of reference. This first volume is so well produced that one cannot help looking forward to the publication of the next four volumes.

H. C. NOHL.

BOOKS RECEIVED

The following books have been received and reviews of some of them will appear in subsequent issues:

L'Acupuncture devant le bon sens et la Physiologie des Points Cutanes Sensibles Couples. By J.-Ph. Crouzet. Paris: Vigot Frères. Pp. 134. Fr.1,300.

Aviation et Tuberculose Pulmonaire. By Pierre Weiller. Paris: Vigot Frères. Pp. 232. Illus.

Les Nouveaux Termes Anatomiques. By A. G. Olivier. Paris: Vigot Frères. Pp. 146. Fr.800.

Die Tuberkulose, Ihre Erkennung und Behandlung. By Hellmuth Deist and Hermann Krauss. Stuttgart: Ferdinand Enke. Pp. 847. Illus. DM.138.

Orthopædic Surgery. 5th edn. By Sir Walter Mercer. London: Edward Arnold Ltd. Pp. 1074. Illus. 90s.

Chest and Heart Disease in the Commonwealth, 1958. London: The Chest and Heart Assocn. Pp. 444. Illus. 35s. or $6.

Bronchography. By C. Dijkstra. Oxford: Blackwell Scientific Publications. Pp. 157. Illus. 45s.

Cardiovascular sound in Health and Disease. By Victor A. McKusick. London: Baillière, Tindall and Cox. Pp. 570. Illus. 120s.

The Ecology of Human Disease. By Jacques M. May. New York: M.D. Publications. Pp. 327. $7.50.

Long-term Prognosis in Pulmonary Tuberculosis detected by Mass Radiography. By Ivan Kallquist. Copenhagen: Ejnar Munksgaard. Pp. 175.

Konservative und chirurgische Behandlung angeborener und erworbener Herzfehler. By E. Derra, O. Bayer and H. H. Wolter. Stuttgart: George Thieme. Pp. 64. DM.6.40.

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REPORTS

COMMITTEE ON RADIOLOGICAL HAZARDS TO PATIENTS

Interim Report

Some brief extracts of the report* are noted, but for exact details and appendices the reader is referred to the report itself.

The Committee was appointed by the Secretary of State for Scotland and the Minister of Health at the end of 1956, its terms of reference being "To review the present practice in diagnostic radiology and the use of radiotherapy in non-malignant conditions, having regard to the report of the Committee on the Hazards to Man of Nuclear and Allied Radiations, and to make recommendations." Lord Adrian was chairman of the Committee.

It has been known for more than fifty years that living cells may be damaged by ionising radiation, and that excessive exposure may cause serious injury to man. In recent years attention has been drawn to two less obvious hazards which may perhaps be produced by relatively low levels of radiation dosage. Experimental work has shown that ionising radiations can induce mutations in reproductive cells and so cause genetic damage to future generations in the species studied. In mankind such damage could lead to a variety of inherited defects.

Secondly, there is a problem concerning the individual—the somatic hazard—which is mainly the risk of leukæmia arising from exposure of the bone marrow to ionising radiations. It is known that this disease can result from very heavy exposure. It is not known for certain whether it ever follows slight exposure or whether there may not be some threshold of appreciable size which must be reached before any risk arises.

The report of the Medical Research Council on the Hazards to Man of Nuclear and Allied Radiations described the sources of ionising radiations to which the human race is subjected, and assessed the contribution made by each source to the total radiation to which the population of this country is exposed. It found that of all the man-made sources, medical and dental radiology contributed much more than any other. The calculation of this contribution had to be based on a relatively small amount of data, but subsequently both the report of the United Nations Scientific Committee on the Effects of Atomic Radiation, and the statement on this report by the Medical Research Council, confirmed this finding.

The Committee has set itself a twofold task: (*a*) to undertake a nation-wide survey of radiological procedures in order to estimate the present level of radiation to which the population is exposed. (*b*) At the same time to consider the particular diagnostic and therapeutic procedures in present use, with the object of eliminating all unnecessary irradiation of the gonads and of the body generally.

Mass Miniature Radiography of the Chest

The importance of mass miniature radiography in Britain may be briefly illustrated by the following statistics. In 1957 a total of 3,451,060 mass miniature radiography examinations were carried out in England and Wales, and during the same year an extensive mass radiography campaign was held in

* Department of Health for Scotland. Radiological Hazards to Patients. Interim Report of the Committee. Published by H.M.S.O. 1959. Price 1s. 3d. net.

Scotland and 1,319,867 examinations were made, amounting in all to 4,770,927. For the whole of Great Britain these examinations led to the discovery of 17,835 cases of pulmonary tuberculosis requiring supervision. Over 63,000 other abnormalities were detected and these included 2,362 cases of lung cancer, nearly 12,000 cardiac abnormalities and 9,400 cases of pneumoconiosis. It is clear that the hazard, if any, of this particular form of radiation exposure must be balanced against the undoubted benefits.

General Comments on Diagnostic Radiology

The Committee feel that it is not likely that in their final report they will have to recommend a drastic reassessment of the place of diagnostic radiology in medicine and dentistry. They emphasise, however, the need to ensure that radiation exposure from this source should be kept to a minimum. They draw attention to the difference between fluoroscopy and radiography. It is not generally realised even among the medical profession that the dose per examination in fluoroscopy is considerably higher than that from radiography. The dose in fluoroscopy should be minimised by adequate dark adaptation on the part of the observer and by the routine use of timing devices. The development and use of image intensification will also contribute to this end. The rigorous application of the recommendations in the Code of Practice for the protection of persons exposed to ionising radiations would play a considerable part in reducing the dosage received by patients.

They state that there should be clear-cut indications before an X-ray examination is requested. Strict control of progress or repeat X-rays is essential.

They stress that all means should be taken continually to ensure that radiation exposure is kept at a minimum. They believe that the level may be reduced appreciably without prejudice to the interest of the patient. Diagnostic radiology by the part that it plays not only in diagnosis but in the correct treatment of the patient renders immense service to medicine and dentistry. There is no doubt that much individual suffering would follow any unnecessary curtailment of those services.

Summary of the Report

(1) A survey has been made of exposure to radiation produced by mass miniature radiography. The doses to the gonads have been found to be less than those previously reported. *It is concluded that properly conducted examinations of this kind make a negligible contribution to the total radiation to which the population is daily exposed.* Even on the most pessimistic assumptions our measurements have shown that indefinite continuation of the present rate of mass miniature radiography could add no more than 20 cases of leukæmia to the annual incidence of 2,500 cases of this disease. On the other hand, mass miniature X-ray examinations in 1957 led to the discovery of nearly 18,000 cases of pulmonary tuberculosis and some 63,000 other abnormalities which included lung cancer, heart disease and pneumoconiosis.

(2) On the principle that all unnecessary exposures should be prevented, the Committee endorse the steps already recommended to reduce even the present small dose, and further recommend that mass miniature radiography should not be used as a case-finding procedure in children or in pregnant women.

(3) The Committee have set out some general principles towards the reduction of unnecessary exposures in other forms of diagnostic radiology.

Brit. J. Dis. Chest (1959) **53**, 332.

NOTES AND NOTICES

FOURTH INTERNATIONAL COURSE ON TOMOGRAPHY, GENOA, SEPTEMBER 28 TO OCTOBER 3

THIS Course, at the Institute of Radiology of the University of Genoa, is under the direction of Professor Alessandro Vallebona. It is proposed to treat tomography in all its aspects at this conference.

DEATHS FROM TUBERCULOSIS AND CANCER, 1958*

CONTINUED FALL IN TUBERCULOSIS DEATHS

THE total number of deaths from respiratory tuberculosis in 1958 was 4,000 against 4,249 in 1957, giving a provisional death rate of 89 per million persons. This is a decrease of just over 6 per cent. compared with the previous year, and means that since 1948 the death rate from respiratory tuberculosis has fallen by nearly 80 per cent.

INCREASED DEATHS FROM CANCER OF THE LUNG

The provisional death rate for all forms of cancer for men was 2,333 per million population, and for women, 1,929. These figures show a slight increase from 1957.

The rate for men increased since 1957 from 759 to 783 per million population for deaths assigned to cancer of the lung and bronchus, and decreased from 1,553 to 1,550 for other forms of cancer. The rate for cancer of the lung and bronchus for women increased from 116 per million in 1957 to 119 in 1958, and increased for other forms of cancer from 1,774 in 1957 to 1,810 in 1958. Male deaths from cancer totalled 50,732, of which 17,030 or over 33 per cent. were certified as due to cancer of the lung and bronchus. For women, out of a total of 45,067 deaths from cancer, only 2,779 or about 6 per cent. were ascribed to this cause. The total number of cases with cancer of the lung and bronchus in males and females was, therefore, 19,309.

AMERICAN HEART ASSOCIATION—NEW RESEARCH FELLOWSHIPS

A BRITISH scientist, Dr. Helmut Mueller, of Cambridge University, and Dr. Werner Straus, of the University of Louvain, Belgium, are among 182 specialists whose work on heart diseases will be supported by the American Heart Association.

The American Heart Association announced that it is awarding $1,562,243 in fellowships as part of its programme to support research aimed at discovering the underlying causes of diseases of the heart and blood vessels.

The fellowships are for the year beginning in July.

Dr. Mueller will continue his research on abnormal heart function, which is often at the root of heart failure, and on inducing relaxation after muscular contraction has set in.

Dr. Straus's research is on the functions of phagosomes, granules found in the cells of heart and blood vessels which are believed to absorb foreign materials entering those organs.

* The Registrar-General's Weekly Return No. 13, 1959. H.M.S.O. 1s. 6d. net.

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A STUDY OF THE INCIDENCE OF BRONCHITIS AMONGST SOME FOUNDRYMEN IN DERBYSHIRE AND NOTTINGHAMSHIRE, COMPARED WITH A CONTRASTING OCCUPATIONAL GROUP, AND A GEOGRAPHICAL STUDY OF BRONCHITIS MORTALITY IN THE FOUNDRY WORKERS OF ENGLAND AND WALES

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PART ONE

Introduction

Many studies on the incidence of bronchitis amongst industrial populations have been carried out in recent years (Pemberton, 1952; Pemberton, 1956; Clifton, 1956; Gregory, 1955; Higgins *et al.*, 1956; Higgins, 1957), but none specifically relating to foundrymen.

A great variety of engineering work, including iron founding, is carried out by the Butterley Company and, in addition, for many years there have been comprehensive arrangements for the supervision of the health of its employees. Accurate records of the incidence of sickness are in existence, so that much material was already available for an investigation of bronchitis between contrasting occupational groups, and it was therefore decided to undertake a study of foundrymen, representing workers exposed to dust, heat and fume, and of the men employed in the building of railway wagons, whose work requires a similar amount of physical exertion but is done in a clear and reasonably equable atmosphere. The general environment of the Butterley foundries is similar to that of most large foundries and has already been described elsewhere (Keatinge and Potter, 1945; Keatinge and Harding, 1954).

In view of the well-known difficulties a definition of bronchitis has not been attempted and, instead, for the purpose of this study certain criteria similar to those used in a Health Survey of Gas Workers in New South Wales (Cummings *et al.*, 1952) were adopted, namely:

(i) The admission by the worker, on questioning, of the presence of a persistent productive cough.

(ii) Incapacity for work due to respiratory disease aggregating 21 days or more between 1947 and 1956, inclusive.

(iii) The presence of abnormal physical signs in the lungs in workers who were known to have suffered from recurrent attacks of cough, whether or not they confessed to a persistent productive cough or had experienced incapacity for work due to respiratory disease as defined above.

(*Received for publication June* 30, 1959.)

The turnover amongst the unskilled workers in the foundries and in the wagon works is rather high, and it was therefore necessary to define the term " foundryman " and " wagon worker " rather precisely; only men of ten years' or more service, including those who had retired from active work, were included in this study. Of ten years' or more standing there were 92 foundrymen of whom 10 were retired, and 67 workers in the wagon shops with 1 man who had retired.

TABLE 1.

TABLE OF AGE GROUPS OF MEN IN THE FOUNDRY AND IN THE WAGON WORKS

Age groups	*Wagon works*	*Foundry*
25–35 years	12	4
36–45 „	16	25
46–55 „	19	30
56–65 „	15	12
65+ „	5	21
TOTAL	67	92

METHOD

The survey fell into several parts:

(i) All the men were interviewed by one observer who asked a series of standard questions; on a subsequent occasion the foundrymen were interviewed by a second observer who put the same questions to them. A complete occupational history was taken if not already known. The men were asked about their wives' health, the number of their children and the condition of their health, the home circumstances and the number of people living in the house. Enquiry was also made about the smoking habits, the presence of cough, and if present its type and incidence, and about previous chest or other illnesses affecting both the men and their wives.

(ii) A review of sickness absence from 1947–56. The recording of sick absences has been based on the 6th and 7th Revisions of the International Classification of Diseases, Injuries, and Causes of Death, and every effort is made to record as exact a diagnosis as possible. Affections of the respiratory system are broken down into the following sub-headings:

1. Upper respiratory infections, including the common cold.
2. Diseases of the nose.
3. Bronchitis and bronchial catarrh.
4. Influenza and its sequelæ.
5. Pneumonia and pleurisy.
6. Tuberculosis.
7. Tonsillitis and throat infections.

In this study the term respiratory illness has been restricted to absences recorded as due either to bronchitis and bronchial catarrh, or to pneumonia and pleurisy. The two last mentioned have been included on the ground that bronchitis, bronchiectasis and bronchopneumonia can represent different stages of the same disease (Pemberton, 1952).

(iii) A consideration of clinical findings. Since all the men who participated in the survey had been continuously employed by the company for ten years or more, many had at one time or another been submitted to comprehensive examination, including auscultation and a postero-anterior X-ray chest film. In addition, the ventilatory capacity of all the men was estimated with the Wright respiratory flow meter (Hugh-Jones, 1957) from the volume of air expelled in 0·75 second during a forced expiration. The result is expressed as the maximum voluntary ventilation (M.V.V. Indirect) in litres/minute by multiplying the volume by 40. All the men regarded as presumptive bronchitics were also examined clinically and were submitted to radiography of the chest during the course of the survey.

(iv) Deaths during the period 1947–56. The certified causes are recorded of all deaths amongst active or retired workers.

Results

Interview and Questionary

There was little agreement between the statements made by the men about their previous illnesses and the facts as shown by the sickness absence records. Thus, out of 8 foundrymen who had lost three weeks or more time due to respiratory illness during the ten years under review, 5 said they had never lost any time due to this cause; while, on the other hand, of 9 who claimed to suffer with a persistent productive cough, only 2 had lost time between 1947 and 1956 as a result of chest illness. Nevertheless, all 5 wagon workers who had been away from work due to chest illness for three weeks or more during the ten years admitted the presence of a persistent productive cough, but there were, in addition, 2 other wagon workers who, though they claimed to have a persistent productive cough, had lost no time due to respiratory illness. However, the questioning of the foundry workers by a second observer showed that there was 25 per cent. discrepancy with the answers obtained by the first observer to questions about health and sickness absence. On the other hand, complete agreement was obtained by both observers about smoking habits and housing conditions, and further checks by interviewing relatives and by

Table 2

	Foundrymen	*Wagon workers*
Total number in survey ..	92	67
Number of presumptive bronchitics	19 (20·6%)	10 (14·9%)

personal visits to the homes, and in other ways, made it clear that reliance could indeed be placed on the statements made by the men about such matters.

In Table 2 a summary of the broad results of the survey are tabulated.

Age Groups

The ages of the foundrymen who were regarded as presumptive bronchitics ranged from 37 to 76 years of age, but of these men only 3 were under 45, and 5 more than 60 years of age. In the case of the wagon workers, the youngest subject was 31 and the oldest 63, and out of the 10 presumptive bronchitics, 2 were more than 60 years of age.

Smoking

The majority of the men smoke, as is seen in Table 3 which shows their smoking habits. Of the 19 foundrymen, 2 did not smoke at all, although in the wagon workers regarded as presumptive bronchitics all 10 were smokers.

Table 3

	Foundrymen	*Wagon workers*
Total number in survey ..	92	67
Cigarette smokers	54 (58·7%)	42 (62·7%)
Pipe smokers	8 (8·7%)	6 (8·9%)
Cigarette and pipe smokers ..	13 (14·2%)	3 (4·5%)
Non-smokers	17 (18·4%)	16 (23·9%)
Total number of smokers ..	75 (81·6%)	51 (76·1%)

Amongst the foundrymen as a whole 17 (18·4%) did not smoke, while the wagon workers had a rather better record with 16 (23·9%) non-smokers.

Housing

There was no evidence of overcrowding and the position is summarised in Table 4. Information was only sought about the housing conditions at the time of the survey and no attempt was made to assess the housing history of these men throughout their life. However, as they all belonged to the lower social levels according to the Registrar-General's Classification (1957)—social class III and below—the type of house occupied by them did not vary greatly. The housing is on the whole of a high order and all the men who participated in

Table 4.—Persons in Household

	Maximum	*Minimum*	*Mean*
Foundrymen ..	9	1	3
Wagon workers ..	7	1	3

this study were in occupation of either detached or semi-detached houses, or those forming part of a terrace. However, even the older terraced houses are generally built in fairly small blocks and all have adequate air space; many also possess gardens, of which some are quite large. Over 90 per cent. of the men had been born in the locality and spent the greater part of their lives in it.

Occupational Histories

Of the foundry workers, 20 had had previous experience in the coal mining industry, nearly all of them for ten years or more, and 5 of these men who were regarded as presumptive bronchitics had worked underground. Thirteen wagon workers had also been employed at some time in the coal mining industry and most of them also for ten years or more. Of the 10 wagon builders classed as presumptive bronchitics, 5 had been previously employed in colliery work and only one of them had spent less than sixteen years underground. In other respects, the occupational histories were irrelevant. Table 5 shows the years of service of the foundrymen and wagon workers, classified into age groups, and it will be seen that the average length of time spent in the foundry industry was 28·9 years per man, whereas in the wagon workers the average period of service per worker was 22·04 years.

Table 5.—Years of Service

Age groups years	10—		20—		30—		40—		50—		60+	
	Foundry-men	*Wagon workers*	*Foundry-men*	*Wagon workers*	*Foundry-men*	*Wagon workers*	*Foundry-men*	*Wagon workers*	*Foundry-men*	*Wagon workers*	*Foundry-men*	*Wagon workers*
25–35	4	12	—	—	—	—	—	—	—	—	—	—
36–45	7	10	18	6	—	—	—	—	—	—	—	—
46–55	6	7	11	3	12	9	1	—	—	—	—	—
56–65	2	5	2	2	4	6	4	2	—	—	—	—
65+	4	2	2	—	5	1	1	—	7	2	2	—
Total	23	36	33	11	21	16	6	2	7	2	2	—

Total years of exposure: Foundrymen .. .. 2,652 years.
Wagon workers .. .. 1,477 years.

Clinical findings

An assessment of the M.V.V. was done for all the men participating in the survey, except two, one a foundryman in active work who could not be persuaded to carry out the test, and a retired foundry worker, aged 77, who was too ill to make the attempt. The results for the groups as a whole and for the bronchitics are shown in Table 6, by age groups, indicating the mean age and measurements of standing height and weight of the subjects.

All the men regarded as presumptive bronchitics had in addition been submitted to recent X-ray and auscultation of the chest. Amongst the 19 foundrymen there were 5 cases in which radiological evidence of early dust changes were seen although no disability was present, but good objective

evidence of bronchitis either clinical or radiographic was found in only 7 (36·8%) people, 6 of whom were over 60 years of age. No changes attributable to dust were detected in the X-ray films of the 10 wagon workers, but objective evidence of bronchitis was present in 6 (60·0%). When the mean M.V.V. (litres/minute) of all foundry workers, including bronchitics, is compared with that of the bronchitic foundry workers alone, it will be seen that, with the exception of the men under 36 years of age (amongst whom no bronchitics were recorded) and those of 56 years and over, the M.V.V. of the bronchitic group is actually the better of the two. On the other hand, in the case of the wagon workers, all the age groups in which bronchitics were recorded had a worse showing than the wagon workers taken as a whole. An assessment of bronchitis based on clinical examination and respiratory function tests therefore shows that the evidence of bronchitis is proportionately greater among the wagon workers than the foundrymen.

Absence from Work due to Respiratory Disease

The loss of time due to respiratory illness experienced by the 92 foundry men in the ten years under review averaged only 0·44 day per annum, but the figure for the wagon workers was nearly twice as great with an average loss of time of 0·78 day per annum. These figures may be compared with 1·77 days lost per annum reported by Gregory (1955) in gas works men exposed to dust.

Deaths

During the relevant period there were 12 deaths amongst men who had been employed for ten years or more in foundry work and of these 4 had retired. In 2 cases only did bronchitis appear on the death certificate and in 1 of them the disease directly leading to death was given as carcinoma of the rectum, and in the other cardiac failure was held to be secondary to chronic bronchitis and emphysema in a man aged 73 years. This man had been examined on a number of occasions over the years in the Medical Department of the company, and electro-cardiography had shown undoubted evidence of myocardial damage: certainly during life there is no doubt that the heart signs dominated the clinical picture. However, in accordance with the classification adopted by the Registrar-General this death must be accepted as " bronchitis " for the purpose of comparison with official figures. Among the wagon workers, 6 deaths took place in men who had been employed ten years or more, and in no instance was bronchitis given as a cause. After the survey had been completed the one retired worker included amongst the wagon workers died and the cause was recorded as carcinoma of stomach with secondary deposits in liver.

PART TWO

Although the question whether occupation or social environment plays the greater part in the causation of bronchitis still remains undecided, Stocks (1935) took the view that, so far as coal miners were concerned, there was no satis-

TABLE 6.—MEAN AGE, HEIGHT, WEIGHT, ETC.

Age groups in years	Numbers				Average age in years				Average height, inches				Average weight, pounds				M.V.V., litres/minute			
	Wagon workers Bronchitics only	Wagon workers Including bronchitics	Foundrymen Bronchitics only	Foundrymen Including bronchitics	Wagon workers Bronchitics only	Wagon workers Including bronchitics	Foundrymen Bronchitics only	Foundrymen Including bronchitics	Wagon workers Bronchitics only	Wagon workers Including bronchitics	Foundrymen Bronchitics only	Foundrymen Including bronchitics	Wagon workers Bronchitics only	Wagon workers Including bronchitics	Foundrymen Bronchitics only	Foundrymen Including bronchitics	Wagon workers Bronchitics only	Wagon workers Including bronchitics	Foundrymen Bronchitics only	Foundrymen Including bronchitics
25–35 years ..	2	12	—	4	32·5	32·4	—	34·7	65·5	66·6	—	66·5	119·0	145·9	—	146·2	90	124	—	137
36–45 ,, ..	—	16	6	25	—	38·8	40·6	39·8	—	66·7	70·0	68·6	—	146·8	161·6	165·2	—	148	146	146
46–55 ,, ..	4	19	5	30	51·7	50·3	50·8	51·2	64·2	66·7	67·0	67·5	136·2	153·9	158·3	160·1	94	104	135	128
56–65 ,, ..	3	15	3	12	61·3	61·6	63·3	59·8	66·6	66·6	65·3	68·2	156·3	157·0	151·3	152·8	78	91	85	110
65+ ,, ..	1	5	5	21	71·0	71·6	71·8	66·9	71·0	69·6	64·6	65·5	210·0	185·0	140·4	145·0	47	99	66	80

factory evidence of an occupational connection to account for the excess of respiratory mortality amongst miners in South Wales compared with that recorded in Nottinghamshire and Derbyshire miners. Stocks, in fact, held that it was the result either of geographical, climatic or environmental differences affecting the populations as a whole. It seemed possible, then, that geographical differences might well explain the high incidence of bronchitis mortality noted amongst foundrymen in general and the low rate found in this Derbyshire Group, and that they might also account for the high death rate due to this cause recorded for the wives of foundrymen. Unfortunately, the Registrar-General's Decennial Supplement does not give the death rates of foundry workers by regions as is done in the case of coal miners, but the Council of Ironfoundry Associations kindly provided information indicating both the number of iron foundries and the number of foundry workers in the various Ministry of Labour Districts. It was not possible, however, to find out the number of employees in any given foundry in any particular place. In addition to the iron foundries, there are just under 100 steel foundries in England and Wales, but no information could be obtained about the numbers employed in them. This study has, therefore, perforce been limited to the populations of iron foundries, although it is unlikely that the conclusions have been affected by the exclusion of the steel foundries, since their number is comparatively

STATISTICAL SUMMARY OF CONCLUSIONS OF GEOGRAPHICAL STUDY

TABLE A

Region	*No. of iron foundries*	*Workers*	*Average number employed*
London and South-eastern: (Administrative County of London, Kent, Middlesex, Surrey, Sussex, parts of Essex and Hertfordshire)	132	7,442	56
Eastern: (Bedfordshire, Cambridgeshire—including Isle of Ely—Huntingdonshire, Norfolk, Suffolk, parts of Essex and Hertfordshire)	68	4,287	63
Southern: (Berkshire, Buckinghamshire, Dorset, Hampshire, Oxfordshire)	54	1,704	32
East and West Ridings of Yorkshire	284	13,262	46
Midlands: (Herefordshire, Shropshire, Staffordshire, Warwickshire, Worcestershire)	383	30,223	79
Northern: (Cumberland, Durham, Northumberland, Westmoreland, North Riding of Yorkshire)	92	7,850	85
North Midlands: (Derbyshire—except High Peak District—Leicestershire, Lincolnshire, Northamptonshire—including Soke of Peterborough—Nottinghamshire, Rutland)	154	17,230	112
South - western: (Cornwall, Devon, Gloucestershire, Somerset, Wiltshire and South Wales)	114	3,141	27
North-western: (Cheshire, High Peak of Derbyshire, Lancashire)	294	15,590	53
Wales: (North)	13	3,318	255
TOTAL (All Districts)	1,588	104,047	65

STATISTICAL SUMMARY OF CONCLUSIONS OF GEOGRAPHICAL STUDY

TABLE B

Total number of foundrymen 104,047
Number of foundrymen living in areas where the Standardised Mortality Rate (S.M.R.) for bronchitis is recorded as above 100 .. .. 60,050 (57%)
This figure is comprised as follows:

District	*S.M.R.*	*Approximate number of foundrymen*	*Percentage of foundrymen to total foundrymen population*
			%
Glamorganshire	128	405	0·3
Monmouthshire	119	216	0·2
Nottinghamshire	109	3,472	3·3
Staffordshire	112	1,343	1·6
Lancashire	112	3,147	3·0
Middlesex	104	616	0·5
London (Administrative County)	153	1,008	0·9
Barnsley	124	329	0·3
Blackburn	127	689	0·6
Blackpool	110	53	0·05
Burnley	136	795	0·7
Burton-on-Trent	132	237	0·2
Chester	114	53	0·04
Doncaster	114	282	0·2
Nottingham	153	1,568	1·5
Preston	124	742	0·7
Rotherham	136	658	0·6
St. Helens	157	265	0·2
Sheffield	114	1,363	1·3
Stoke-on-Trent	156	1,975	1·9
Warrington	134	440	0·4
West Hartlepool	134	166	0·1
Wigan	193	583	0·5
Northampton	107	448	0·4
Sunderland	120	830	0·8
Cardiff	128	324	0·3
Swansea	127	216	0·2
Tyneside Conurbation	115	2,490	2·3
Yorkshire Conurbation	134	7,144	6·8
Lancashire Conurbation	159	7,791	7·4
Merseyside Conurbation	130	106	0·1
West Midlands Conurbation	134	14,416	12·7
Greater London	123	3,248	3·6
Yorkshire (West Riding)	109	2,632	2·5

small and their distribution follows much the same pattern as that of the iron foundries. Search of a Trade Directory (Rylands, 1954) enabled iron foundries to be located and it was now possible to tabulate foundries all over England and Wales by conurbation, county borough and administrative county. A rough estimate of workers in each foundry was then made by obtaining an average figure from the number of men employed and the number of foundries returned for each district, and on this basis an approximation of the foundry

populations in the different areas was worked out. All the conurbations, county boroughs and administrative counties in which the standardised mortality rate for bronchitis is recorded as above 100 (Registrar-General, 1951) have been regarded as having a high death rate due to this cause, and applying this criterion it is found that 57 per cent. of foundry workers live in areas where there is an excess death rate due to bronchitis, while there are only 43 per cent. in areas with a low mortality from bronchitis.

Discussion

In this small sample of 92 foundrymen compared with 67 wagon workers there is little evidence to support the generally held belief that bronchitis is a common condition in foundrymen: indeed, if anything the morbidity of the wagon workers due to bronchitis is proportionately the greater.

It has been demonstrated that the Butterley workers are not subject to overcrowding in their housing conditions, and indeed it can be said that they are of a high standard in contrast with those reported in Sheffield (Pemberton, 1953). Many of the houses are owned by the Butterley Company and their proper maintenance is a first concern of its Estates Department: in addition, the districts where the men live, although somewhat urbanised, can be regarded as essentially rural in character and to that extent probably freer of atmospheric pollution than is the case in the great conurbations and many of the county boroughs. Most of these workers are also countrymen at heart, and in their hobbies often follow rural pursuits which, apart from being healthy in themselves, frequently enable them to enjoy a fresher and more varied diet than their fellows in the towns, and it is felt that this combination of factors may have contributed to the relative freedom from " bronchitis " which has been observed in this Survey.

Although most of the men smoked, the use of tobacco does not seem to have played a great part in causing " bronchitis " in the connotation accorded to this condition for the present purpose.

A study of the geographical situation of iron foundries and the death rates due to bronchitis amongst the general population in the different areas shows that the majority of foundry workers live in areas where there is an excess mortality due to bronchitis, and it is suggested that this is the explanation of the high mortality figures returned for foundry workers and their wives.

Conflicting opinions have been expressed about the role played by dust in the causation of chronic bronchitis. Higgins *et al.* (1956) studied respiratory disability in Leigh, Lancashire, and concluded that miners and ex-miners had significantly more chronic bronchitis and a lower ventilatory capacity than men who had never worked in the mines, and the assumption was that this was the result of the dusty nature of the miners' work. But " miners " vary greatly in the concentrations of dust to which they are exposed, and in the absence of a definition of the term " miner " the extent to which these men were exposed to a dusty environment is hard to assess. Higgins (1957) surveyed respiratory symptoms and bronchitis in the vale of Glamorgan and found that

the prevalence of chronic bronchitis was higher in those men who had worked in mining or quarrying, and this also was held to be the result of the inhalation of dust at work.

Gregory (1955), in a survey of 168 gas workers at Dudley, held that there was a high incidence of bronchitis in men exposed to dusty conditions, but the numbers studied were small and the criterion of dustiness of the various occupations appears to have been somewhat arbitrary.

Cummings *et al.* (1953), in an investigation into the health of employees engaged in gas production in New South Wales, gave the very guarded opinion that " amongst all groups exposed to dust there appeared to be a tendency to an increased incidence of chronic bronchitis. . . ." but the tendency can hardly be regarded as highly significant, since it did not reach a 1 per cent. level as compared with " other populaces."

Pemberton (1953), in a review of bronchitis in an industrial community, gives figures of sickness absence due to bronchitis amongst workers in four Sheffield steel works in which fettlers and furnace builders (who are exposed to high dust concentrations in their jobs) show a greater incidence of bronchitis than other workers. But the figures given only cover the months of January to June in a single year and, moreover, the foundrymen in general as opposed to the fettlers and furnace builders showed an incidence of bronchitis but little greater than that of all the workers taken together. Again, Pemberton (1956) compared a group of coal miners with two groups of industrial workers and held that chronic bronchitis, emphysema and bronchial spasm were commoner in miners than in the industrial workers, whereas Zwi and Becklake (1958) could find no conclusive evidence of an increased respiratory disability in a mining group compared with a group of railway workers.

If dust is indeed a factor in the causation of bronchitis it is hard to understand why this should be so. After all, the smaller particles pass into the alveoli while most, if not all, of the larger particles of dust are either prevented from entering the air passages or are rejected by the natural defences of the body (Davies, 1949 and 1952) and therefore can hardly be regarded as a cause of bronchitis however much they may aggravate an established condition. Moreover, Pemberton and Goldberg (1954) showed that, although there was a statistically significant association between the death rates due to bronchitis amongst men over 45 in the county boroughs of England and Wales, and the average sulphur dioxide pollution in the years 1950, 1951 and 1952, the association with bronchitis mortality was less consistent when total solid matter deposited was used as the index of pollution.

A small but not unimportant side issue which has arisen in the course of this study is the validity of the answers obtained on questioning presumably healthy men. Agreement between observers in this Survey was comparable with that reported by Fletcher (1956) and Schilling *et al.* (1955), but even a discrepancy of 25 per cent. can hardly be regarded as negligible. More important, however, so far as sickness experience was concerned, the information given by the men, when checked by sickness absence records, was certainly too inaccurate to be of value and this is in accordance with findings reported by

Wood (1958). On the other hand, the answers to objective questions about smoking habits and housing conditions seemed to be correct. This is what might have been expected, since the questions were essentially factual, but the validity of the answers to questions about such subjective matters as the presence or absence of cough and its nature must surely be open to doubt. Apart from the interpretation put by the individual on what is meant by " cough " and by " phlegm " there is, in addition, the inherent wish of most people to be thought well of and to be looked upon as " whole " and this must colour their answers to some extent. Although it can justly be claimed that the men who were questioned in this Survey had confidence in the observers who were well known to them, yet in spite of this fact and careful reassurance, suspicion about the true motives of the questionary was sensed on more than one occasion. Any experienced physician or nurse—especially in industry—is familiar with this sort of reaction, and when confronted with a novel situation the answers of the less well educated and less intelligent are often conditioned by their fears. Again it is a commonplace that unpleasant experiences in the past are often consigned to some limbo of the mind where they are conveniently forgotten, or at best but half remembered. May not this account for the discrepancies noted between the answers given to questions about past illness and the sickness record? In short, how far can reliance really be placed on the answers to questions about health, however tactfully they are put, to people who do not consider themselves ill, and however well trained and careful may be the observers.

Summary

Morbidity and mortality due to bronchitis have been studied amongst a group of foundrymen representing workers exposed to dust, heat and fume, compared with a group of wagon builders whose work is done in an equable, clear atmosphere. Only men of ten years' or more service have been included in the Survey.

Little evidence was found to support the generally held belief that bronchitis is a common condition in foundrymen.

A geographical study of bronchitis mortality in foundry workers of England and Wales was also carried out.

It is estimated that 57 per cent. of foundry workers live in areas where there is an excess death rate due to bronchitis, and it is suggested that geographical situation rather than occupation is the cause of the high bronchitis mortality returned for foundry workers and their wives.

The role played by dust in the causation of chronic bronchitis is discussed.

The answers given by apparently healthy men to a questionary used in this study suggests that the results obtained by this method of investigation may be of doubtful validity.

This survey has only been possible as a result of team work in which all the members of the Butterley Medical Department have participated in one way or another, and their help is gratefully acknowledged. Thanks are also due to all the Butterley workmen who so cheerfully and at some inconvenience submitted themselves to repeated questioning, respiratory

function tests, clinical examinations, and X-rays of chest. Many friends are thanked for helpful criticism and advice, especially Dr. L. G. Norman, Dr. A. I. G. McLaughlin of the Industrial Medicine Research Department of the London Hospital, Dr. J. Watkins-Pitchford, and Dr. P. Weyman, Medical Officer of Health for the Urban Districts of Alfreton, Ripley, Heanor and Ilkeston.

REFERENCES

CLIFTON, M. (1956): *Trans. Ass. industr. med. Offrs.*, **6,** 66.

CUMMINS, C. J., DUNN, T. L., RAYNER, H. E. G., SULLIVAN, J. L. (1953): "An investigation into the health of 625 employees engaged in Gas Production in New South Wales." Division of Industrial Hygiene of Department of Public Health, Sydney, New South Wales.

DAVIES, C. M. (1949): *Brit. J. industr. Med.*, **6,** 245.
(1952): *Brit. J. industr. Med.*, **9,** 120.

DEPARTMENT OF SCIENTIFIC AND INDUSTRIAL RESEARCH (1955): "The Investigation of Atmospheric Pollution." 27th Report. London: H.M.S.O.

FLETCHER, C. M. (1956): *Trans. Ass. industr. med. Offrs.*, **6,** 61.

FRY, J. (1954): *Brit. med. J.*, **1,** 190.

GREGORY, J. (1955): *Trans. Ass. industr. med. Offrs.*, **5,** 2.

HIGGINS, I. T. T. (1957): *Brit. med. J.*, **2,** 1198.

HIGGINS, I. T. T., OLDHAM, P. D., COCHRANE, A. L., and GILSON, J. C. (1956): *Brit. med. J.*, **2,** 908.

HUGH-JONES, P. (1957): "Symposium for Consultants on Industrial Pulmonary Disease." London: Post Graduate Medical School.

KEATINGE, G. F., and POTTER, N. M. (1945): *Brit. J. industr. Med.*, **2,** 125.

KEATINGE, G. F., and HARDING, H. E. (1954): *Brit. J. industr. Med.*, **11,** 298.

PEMBERTON, J. (1952): *Med. Officer*, **88,** 939.
(1953): *Trans. Ass. industr. med. Offrs*, **3,** 202.
(1956): *Arch. industr. Hlth*, **13,** 529.

PEMBERTON, J., and GOLDBERG, C. (1954): *Brit. med. J.*, **2,** 567.

REGISTRAR-GENERAL (1957): Decennial Supplement Part II, Vol. I. Occupational Mortality, England and Wales, 1951. London: H.M.S.O.
(1958): Decennial Supplement, Area Mortality, 1951. London: H.M.S.O.

RYLAND'S COAL, IRON, STEEL, TINPLATE, METAL, ENGINEERING, FOUNDRY, HARDWARE, and ALLIED TRADES DIRECTORY (1954): London: *Iron and Coal Trades Review.*

SCHILLING, R. HUGHES, and DINGWALL FORDYCE (1955): *Brit. med. J.*, **1,** 65.

STOCKS, P. (1935): *J. industr. Hyg.*, **17,** 217.

WOOD, C. H. (1958): *Trans. Ass. industr. med. Offrs*, **8,** 67.

ZWI, S., and BECKLAKE, M. R. (1958): *Brit. J. industr. Med.*, **15,** 258.

Brit. J. Dis. Chest (1959) **53**, 346.

TREATMENT OF RADIATION PNEUMONITIS WITH PREDNISOLONE

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Although radiation pneumonitis was first described as early as 1922 by Groover, Christie and Merritt, only in recent years have other than symptomatic measures been available in the treatment of this condition. The control of superadded infection, to which patients with established radiation damage are prone, became possible with the development of antibiotics but had little effect on the prognosis; a few patients with severe fibrosis mainly confined to one lung have undergone surgical resection (Bergmann and Graham, 1951), but this has not been applicable to the majority of cases.

The use of corticosteroid therapy gave promise of a great advance in the treatment of radiation pneumonitis. In 1951 Cosgriff and Kligerman reported the use of ACTH and cortisone in a 68-year-old woman who developed radiation pneumonitis following therapy for a solitary lung metastasis from a carcinoma of colon. Treatment with ACTH was begun 7 weeks after completion of radiotherapy. A dramatic relief of symptoms occurred within 48 hours and improvement continued during the 30 days ACTH was given. Considerable improvement in the radiographic changes was also observed. During the week after ACTH was discontinued, however, there was progressive clinical deterioration with return of dyspnœa, though no change occurred in the chest radiograph. Corticosteroid treatment was, therefore, resumed, this time using cortisone. Improvement was again noted, though this was slower and less marked than with ACTH. The total duration of corticosteroid treatment was just under 2 months and no immediate symptomatic relapse followed its withdrawal. Two months later, however, the changes of fibrosis were evident in the chest radiograph.

In 1953 Bluestein and Roemer reported the treatment of radiation pneumonitis occurring in " a virgin lung which had not been affected by carcinoma, arteriosclerosis or infection." The patient was a 45-year-old female who suddenly developed dyspnœa and cough following radiotherapy for carcinoma of the breast. The radiographic appearances were consistent with radiation pneumonitis. Treatment with cortisone was begun at once and continued for 3 weeks. Improvement was noted within 24 hours and after one week all symptoms had subsided. One month after treatment was discontinued cough recurred, but responded to a further course of cortisone. Three months after beginning treatment the chest radiograph was normal. From experience with this and other cases the authors stressed the importance of early treatment, maintenance of treatment with high dosage of cortisone for at least 4 weeks, with a total duration of treatment of at least 6 to 8 weeks.

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Subsequent contributions have given conflicting views on the value of corticosteroids, both in the prevention of radiation pneumonitis and in its treatment. In 1954 Freidenberg and Rubenfeld reported the use of cortisone in the prevention of radiation pneumonitis. Though admitting that a precise evaluation of the problem is not possible until the incidence of pulmonary fibrosis following irradiation is known, these writers felt that the results of their study of 9 patients suggested that cortisone may be of value in inhibiting post-radiation pulmonary fibrosis. They also recorded a case with established pneumonitis treated with cortisone for 36 days which showed symptomatic improvement but no marked change in the radiographic appearances. Whitfield, Bond and Arnott (1954) recorded the treatment of 4 patients with ACTH or cortisone. In two cases remarkable improvement resulted but the other two died from respiratory failure. Chu, Nickson and Uzel (1956), reporting the largest series so far (15 cases), were unable to find definite evidence of protection against the development of pneumonitis by ACTH or cortisone, and, though some patients with established pneumonitis benefited symptomatically from these drugs, no appreciable radiographic improvement was noted in the majority.

With such diverse opinions expressed on the value of corticosteroids in the prevention and treatment of radiation pneumonitis, only a controlled clinical trial would give an early answer to the problem. Although this might be justifiable in attempting an assessment of the *preventive* action of corticosteroids it is difficult to justify a trial of corticosteroids in the treatment of developed pneumonitis. In a condition such as radiation pneumonitis which, if severe, can lead to crippling respiratory insufficiency or even death, the failure to use a form of treatment which carries with it no great hazard and which has shown clearly beneficial results in some cases amounts to a denial of treatment. It follows, therefore, that only from a study of recorded experience will it be possible to determine the value of corticosteroids and the best way to use them. The present series of 4 cases is a small contribution to this experience.

Case 1. Mrs. H. M., æt. 27. This patient came under observation in April 1956 following the discovery at routine mass radiography of a large mass in the upper mediastinum. A presumptive diagnosis of lymphadenoma was made and a radical course of wide field radiation was given to the thorax over a period of 7 weeks to a total dosage of 3,000 rads at 250 kV, over 33 treatments. At the end of treatment there was considerable reduction in size of the mediastinal mass.

Three weeks after the last X-ray treatment she began to have a dry cough and slight exertional dyspnœa, which over the next 6 weeks became progressively more severe and was finally present in a distressing degree at rest. She was admitted to hospital at this stage when she was severely breathless at rest with a respiratory rate of 38 per minute and obvious cyanosis. She demonstrated well the sudden arrest of full inspiration to which the name "door-stop" breathing has been applied (Fig. 1). The chest radiograph showed extensive bilateral shadowing (Fig. 2*) and at first the possibility of a recurrence of reticulosis was

* The figures referred to, other than those in the text, appear on Plates XLVIII-XLIX.

considered. This was rejected in favour of radiation pneumonitis because of the rapid development of the radiographic changes so soon after completion of treatment, and it was decided to begin treatment with corticosteroids.

Prednisolone was given initially in high dosage (50 mg. per day) and thereafter progressively reduced, treatment covering in all a period of 27 weeks. ACTH was given every 2 weeks to maintain adrenal function.

Within 48 hours of the start of treatment there had been a striking improvement in the dyspnœa and cyanosis, and the respiratory rate had returned to normal. In 10 days the patient was walking about the ward without distress.

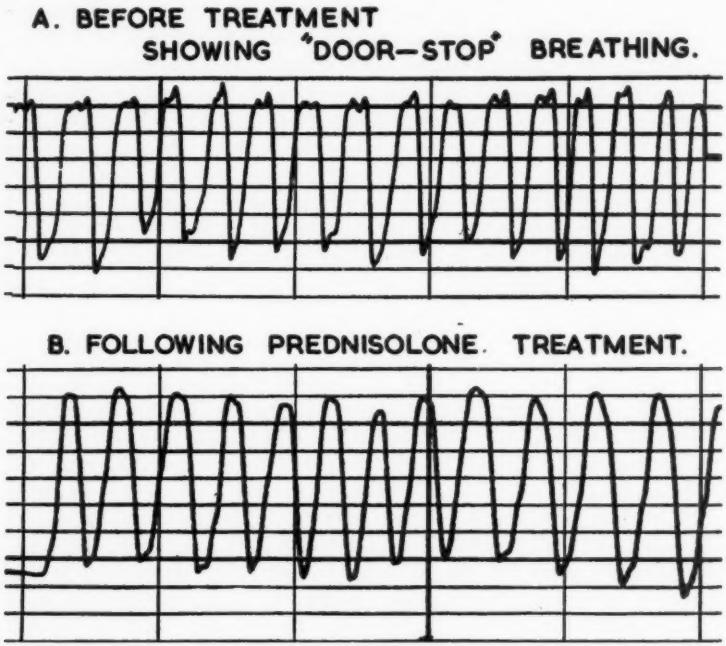

FIG. 1.—Resting Respiratory Pattern. Case H.M.

She was discharged from hospital after 6 weeks to continue treatment at home. Her ventilatory function steadily improved (Fig. 3) and 5 months after the start of treatment she had no residual disability. In fact she was able to take part in, and enjoy, country dancing. The chest radiograph became stable 20 weeks after beginning treatment and has remained unchanged since, showing minor residual fibrosis (Fig. 4). The patient remains well 2½ years after withdrawal of prednisolone. Moderate facial mooning and a disturbing degree of acne were present during the earlier months of treatment, but these rapidly subsided when it was discontinued.

CASE 2. J. H., æt. 28. In March 1955 this patient had an orchidectomy for histologically proven seminoma. Routine post-operative irradiation was given to the abdominal glands. He remained well until June 1956, when he

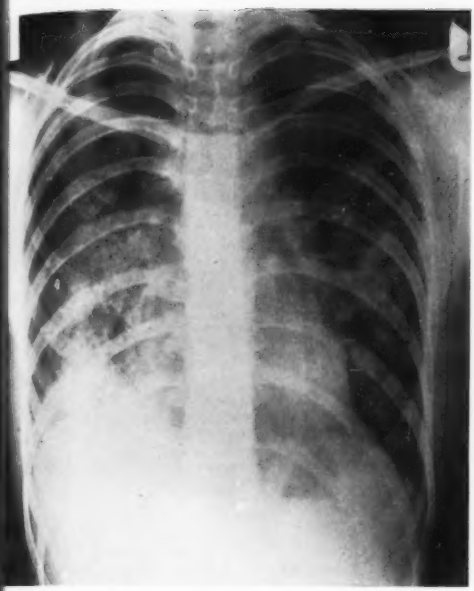

FIG. 2.—Case 1 (H.M.) Chest radiograph at beginning of treatment.

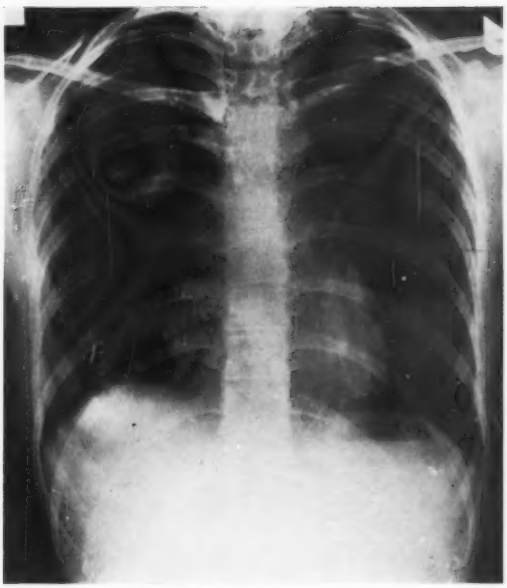

FIG. 4.—Case 1 (H.M.) Chest radiograph after treatment, showing slight residual fibrosis.

FIG. 5.—Case 2 (J.H.) Chest radiograph at beginning of treatment.

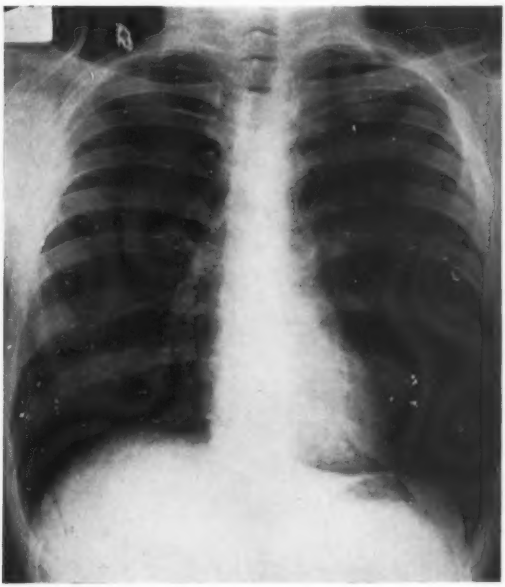

FIG. 7.—Case 2 (J.H.) Normal chest radiograph after treatment.

To face p. 348

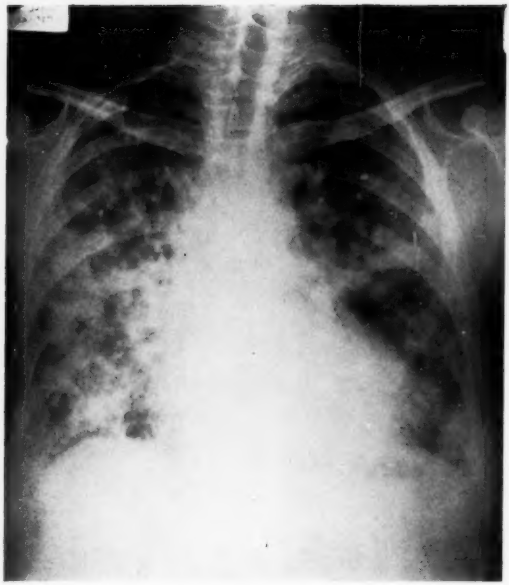

FIG. 8.—Case 3 (B.H.) Chest radiograph at beginning of treatment.

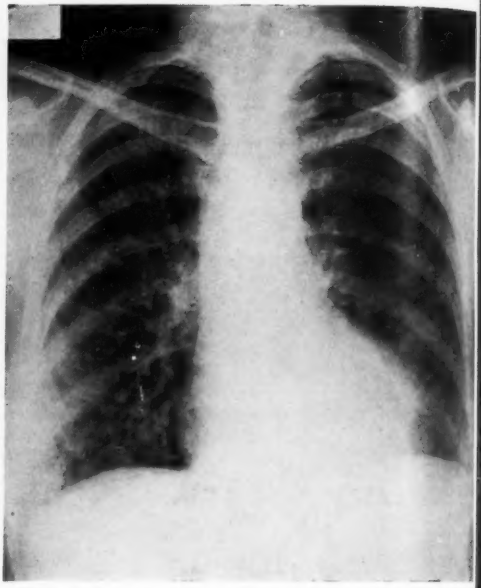

FIG. 9.—Case 3 (B.H.) Chest radiograph showing maximum degree of clearing achieved.

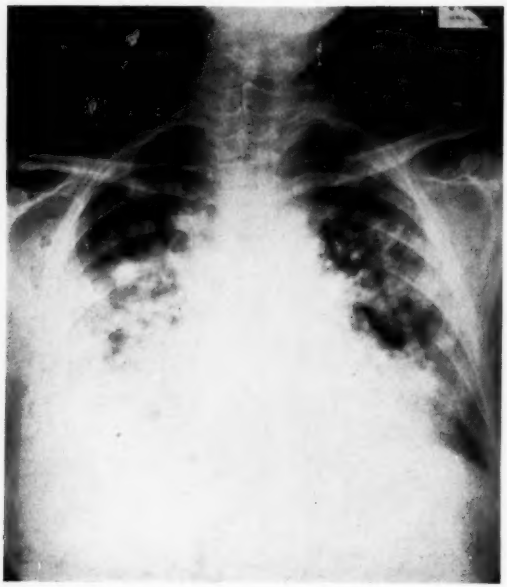

FIG. 10.—Case 3 (B.H.) Chest radiograph showing diffuse infiltration with lymphadenoma.

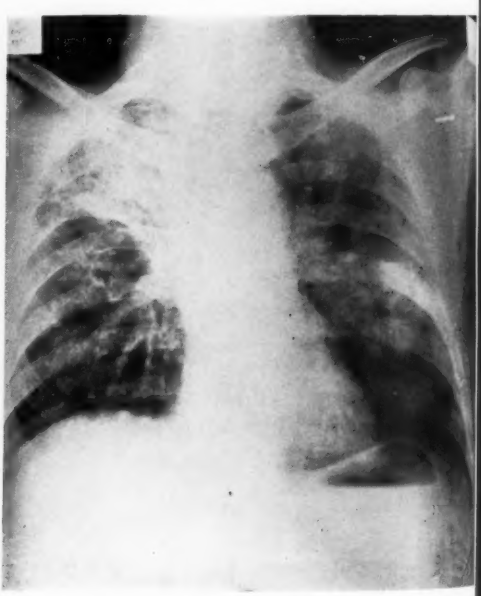

FIG. 11.—Case 4 (P.T.) Chest radiograph at beginning of treatment.

developed rapidly progressive dyspnœa. The chest radiograph then showed massive mediastinal glandular metastases and collapse of the right middle and lower lobes. Over the next 7 weeks wide field radiation was given to the thorax, to a total dosage of 2,150 rads at 250 kV over 34 treatments.

At the end of treatment his exercise tolerance had virtually returned to normal, but 3 weeks later he began to be breathless again. Dyspnœa became rapidly more severe and finally was present at rest. As a result he was confined to bed for the next 6 weeks. A chest radiograph 3 weeks after radiotherapy was

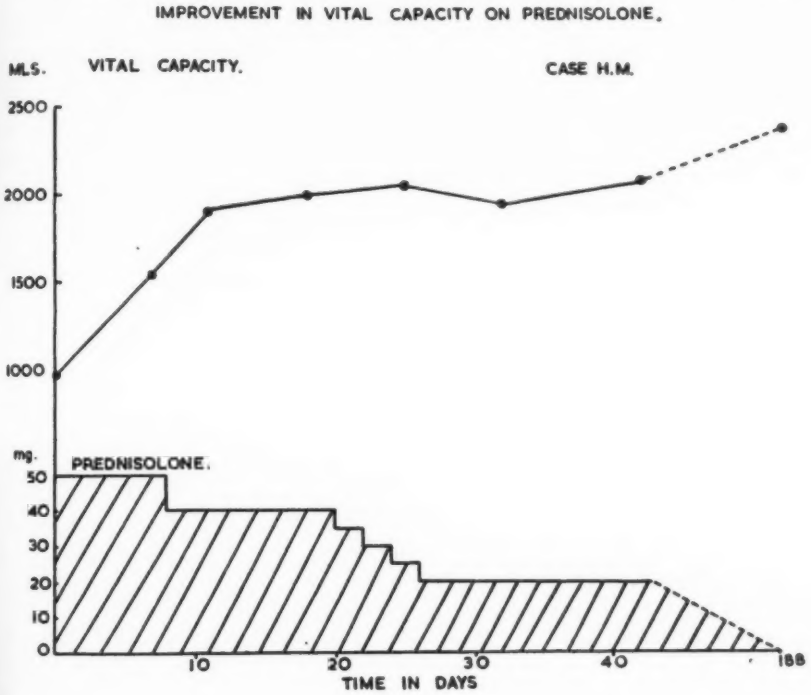

FIG. 3

completed, *i.e.* when dyspnœa began, showed no pulmonary abnormality such as could be ascribed to radiation, but diffuse bilateral changes of that type were present in a film taken a month later (Fig. 5).

Treatment with cortisone was begun on the recommendation of the Radiotherapy Unit and he received 100 mg. of cortisone for 3 days, 75 mg. for 4 days and 50 mg. for 16 days, at which time he was referred to the Northern General Hospital. Even on these relatively small doses of cortisone the patient experienced considerable relief, which had been evident within a few days of beginning treatment, and the chest radiograph showed improvement. Nevertheless, when seen at the Northern General Hospital he still had considerable dyspnœa, although there was no cyanosis at rest. Breathing was of the classical "door-stop" type and chest expansion was poor. The radiographic appearances

had improved but there was still well-marked evidence of pneumonitis. He had obviously not achieved maximum benefit and it was therefore decided to resume corticosteroid therapy, this time in the form of prednisolone on an out-patient basis.

Prednisolone was given in a dose of 40 mg. daily initially, with gradually reducing dosage thereafter, treatment extending over a period of 18 weeks. ACTH was given at fortnightly intervals throughout. Because of the rapid clinical response seen in Case 1 an attempt was made to demonstrate this by ventilatory function tests. These were performed at the beginning of treatment with prednisolone and again 3 days later, by which time clinical improvement

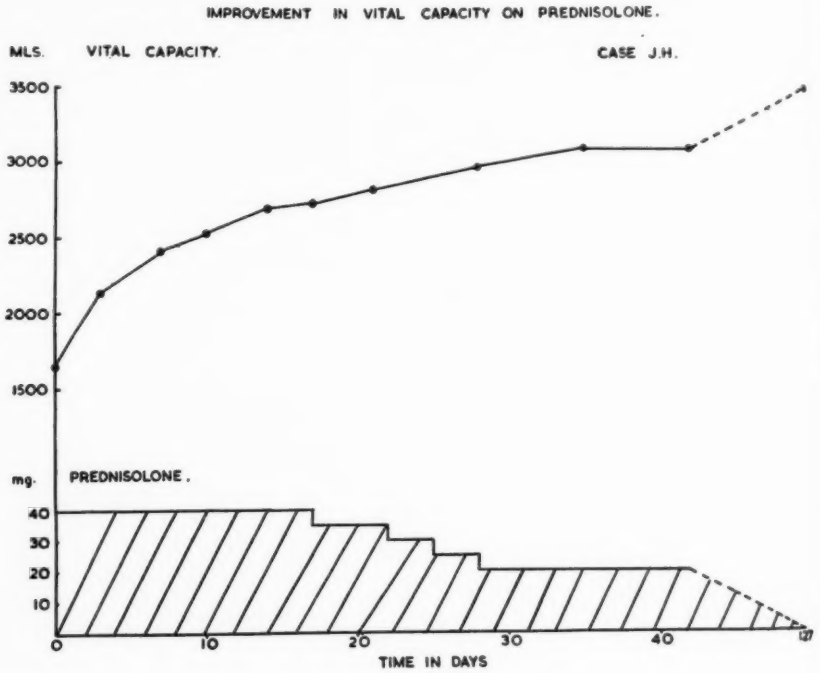

FIG. 6

was evident. The vital capacity showed an increase from 1,650 ml. to 2,140 ml. over this period. Six weeks after beginning prednisolone the patient was entirely free of dyspnœa, even on strenuous exertion. Corresponding improvement was seen in serial function tests (Fig. 6) and chest radiographs. Twenty-eight days after beginning prednisolone and 51 days after beginning cortisone the chest radiograph was normal (Fig. 7). The only complications of treatment were a mild degree of facial mooning and acne during the first few months.

The patient has remained well for 2½ years with no recurrence of dyspnœa and no radiographic deterioration. He now regularly takes part in week-end motor-cycle hill trials.

CASE 3. B. H., æt. 44. This patient was admitted to another hospital in July 1957 with cough, swelling of the face and prominence of the veins over the upper chest, of 2 months' duration. A lymph node removed from the neck was reported as showing lymphadenoma. The chest radiograph showed an anterior mediastinal mass. She was therefore given wide field deep X-ray therapy to include the whole chest, supraclavicular regions and axillæ, receiving an incident dose of 2,500 rads at 250 kV over 33 treatments. At the end of treatment the mediastinal mass was much smaller and a node previously present in the right axilla was no longer palpable. Radiotherapy was given from 6.8.57 to 23.9.57

At the beginning of December she began to have a dry cough and to feel easily breathless on exertion. Over the next 3 weeks dyspnœa became exceedingly severe even at rest and the patient felt as if her chest were circled by bands which would not let her take a deep breath. On 2.1.58 the chest radiograph showed diffuse opacities of the type seen in radiation pneumonitis (Fig. 8).

She was admitted to the Northern General Hospital on 15.1.58, when physical examination revealed slight cyanosis and tachypnœa at rest (respiratory rate 28 per minute) and an obvious abrupt halt to full inspiration. The vital capacity was markedly reduced to 850 ml. (predicted 3,170 ml.).

Treatment was begun with prednisolone 40 mg. daily, on 16.1.58. Within 36 hours the patient volunteered improvement and with each successive day she felt progressively more capable of respiratory effort. Serial function tests showed progressive improvement in the vital capacity, which had doubled by the sixth day of treatment. At the same time chest radiographs showed progressive clearing of the diffuse pulmonary opacities.

Prednisolone was given in a dose of 40 mg. daily from 16.1.58 to 5.2.58 and 30 mg. per day from 6.2.58 to 13.2.58. She was then discharged from hospital and continued treatment at home with 20 mg. prednisolone daily. Though considerably improved the chest radiograph still showed substantial shadowing (Fig. 9). Up to this time function tests had shown a steady increase in vital capacity, but thereafter a slow deterioration occurred. No further improvement was seen in the chest radiograph and 2 months after discharge the diffuse pulmonary opacities, particularly those on the left side, became more prominent and assumed a nodular character. Clinical evidence of resurgence of the original disease was discovered at this time in the form of enlarged glands in the left axilla. This was attended by pain in the arm, and a further course of radiotherapy was given to the left axilla and supraclavicular region with a satisfactory response.

Nevertheless she remained reasonably well with little complaint of dyspnœa until June 1958, when an attempt was made to reduce the dose of prednisolone from 20 mg. to 15 mg. daily. This was followed by lassitude and slight dyspnœa which abated when the dose was increased to 20 mg. daily. In July a respiratory infection necessitated temporary increase in the dosage of prednisolone to 40 mg. per day until the infection was controlled, and in September she developed a staphylococcal septicæmia which responded to antibiotics and increase in the dosage of prednisolone. Throughout this time the chest radiograph had shown slow deterioration with the development throughout both lungs of enlarging nodular opacities, and it was now considered likely that the appearances were due to infiltration with lymphadenoma.

In October the patient's general condition began to deteriorate with general

weakness and return of disabling dyspnœa. Extra-thoracic progression of the primary disease had occurred with the development of further glandular swellings in the neck, axillæ and groins, and though increase of the prednisolone dosage to 40 and finally 50 mg. per day had some subjective ameliorating effect, it was obvious that corticosteroid therapy was no longer influencing the deterioration in respiratory function. After several weeks of increasing dyspnœa the patient died of respiratory insufficiency on 6.12.58. A final chest film on 4.12.58 had shown further deterioration in all zones (Fig. 10).

At autopsy there was widespread involvement with lymphadenoma of lymph nodes, bone marrow and both lungs. The lungs showed scattered nodules of pale, firm tumour up to 2 cm. in diameter which had no particular relation to hilum, bronchi or pleura. The microscopic sections of the lungs showed lymphadenoma together with "lipid pneumonitis" and a moderate amount of interstitial fibrosis. The pathologist commented that the latter may have represented a radiation pneumonitis component, but that the differentiation of two sclerosing lesions was not possible.

Case 4. P. T., æt. 56. This patient, a coal miner all his working life, was well, apart from symptoms of mild chronic bronchitis, until September 1957, when he developed a sore throat and hoarseness and noticed for the first time a swelling in the neck. A clinical diagnosis of carcinoma of the thyroid was made and, following preliminary radiotherapy to the gland, a right hemithyroidectomy was performed. The pathological specimen proved to be a poorly differentiated adeno-carcinoma. Prophylactic wide field radiotherapy to the thorax was then given from 2.10.57 to 8.11.57 to a total of 2,450 rads at 250 kV. At the end of this treatment the patient developed a cough with mucopurulent sputum for which a 7-day course of tetracycline was given with little effect. The chest radiograph at this time, apart from showing early simple pneumoconiosis, was negative, but by 22.11.57 streaky shadowing had appeared in both upper lung zones and throughout the next few weeks the radiographic changes became more extensive, finally involving all lung zones (Fig. 11). With the development of the lung changes the patient experienced increasing exertional dyspnœa, so that when referred to the Northern General Hospital on 7.1.58 he was breathless on the slightest exertion. The vital capacity was reduced to 1,160 ml. (predicted 3,170 ml.).

A diagnosis of radiation pneumonitis was made and treatment was begun with prednisolone 40 mg. daily. The sputum was mucoid in character at this stage and no specific organism was isolated on culture. Nevertheless, because of the recent history of recurring pus in the sputum tetracycline was also given in 1½ G. daily dosage. On this régime the vital capacity had increased to 1,720 ml. by the fourth day, and by the twelfth day of treatment further increases in vital capacity had been recorded. The prednisolone dosage was thereafter reduced by 5 mg. daily over the next 4 days, 20 mg. being given from 23.1.58 onwards.

Seven days after the start of treatment pus again appeared in the sputum and continued intermittently over the next few weeks. Radiographic improvement thus far had been disappointing in spite of the improvement in respiratory function. On 24.1.58 a routine radiograph showed the development of a shallow right upper pneumothorax, unexpected because of the early obliteration of the pleural space in most cases of radiation pneumonitis. By 12.2.58 the pneumothorax had spontaneously absorbed but recurred on 20.2.58.

With the development of frank pus in the sputum on 27.1.58 penicillin was begun (6 mega units daily) and continued until 20.2.58. This was effective initially in clearing the sputum of pus, but in spite of this the patient's general condition began to deteriorate and he again began to complain of exertional dyspnœa. Repeated vital capacity recordings confirmed the deterioration in respiratory function. On 15.2.58 pus again appeared in the sputum and on 20.2.58 chloramphenicol was substituted for penicillin following the repeated culture from the sputum of *Staph. pyogenes* sensitive to chloramphenicol and erythromycin only. In spite of this and increase in prednisolone dosage to 60 mg. daily from 13.2.58 onwards, dyspnœa became progressively worse and on 2.3.58 the patient died of respiratory insufficiency. A final chest radiograph on 26.2.58. had shown absorption of the pneumothorax. The initial slight improvement in the pulmonary opacities had not been maintained and the final film showed generalised slight deterioration compared with that at the start of treatment.

At autopsy no evidence of malignancy was found in the thyroid or elsewhere in the body. Examination of the respiratory system was reported as follows:

"Larynx, trachea and bronchi showed no abnormality beyond some mucosal congestion. There was slight excess of transudate in each pleural sac. There were no pleural adhesions. The right lung weighed 830 G. and the left 730 G. Sectioning revealed similar changes in both lungs. In each upper lobe there was diffuse fibrosis and blackening by carbon pigment. The middle and lower lobes showed evidence of diffuse pneumonitis without complete consolidation. Grey-brown areas were present on a red background. There appeared to be no tumour invasion of lung and the hilar lymph nodes were not enlarged. Changes were consistent with post-radiation pneumonitis and fibrosis.

Microscopy. Lungs: The abnormalities in the lungs show considerable variation from one area to another. Comparatively little normal lung survives and such unconsolidated lung as there is tends to be emphysematous. Otherwise most inter-alveolar septa show some degree of thickening. Some of the alveoli are occupied by polymorphonuclear inflammatory exudate, others by fibrin and others by fibrous tissue which may extend from one alveolus to the next through gaps in the septa. Some small areas of lung show diffuse fibrosis heavily pigmented by carbon and it is possible that this fibrosis preceded radiotherapy or was only exaggerated by radiotherapy. Many of the bronchi are dilated and occupied by mucopus. The bronchiolar epithelium is often hyperplastic and the alveolar epithelium frequently shows cubical metaplasia. There is some calcification of small vessels but the large vessels show no gross damage or evidence of former thrombosis.

These lungs show more evidence of pyogenic inflammation than is usually described in post-radiation fibrosis; without the history it might be difficult to distinguish the lesion from a primary infective pulmonary inflammation."

Discussion

Though improved radiotherapeutic technique has reduced the incidence of radiation pneumonitis, despite a trend toward higher radiation dosage, this condition is by no means uncommon, especially following wide field treatment to the thorax. In a severe form radiation pneumonitis is attended by dyspnœa which may be extreme, and death from respiratory insufficiency has been

reported within a week of the onset of symptoms (Whitfield *et al.*, 1956). As congestion and œdema characterise the early stages it was logical that corticosteroids, because of their marked anti-inflammatory effects, should be tried in treatment. That these drugs can exert a profound beneficial influence, in at least some cases, has already been clearly demonstrated, and the early and dramatic response in Cases 1 and 2 in the present series cannot be interpreted otherwise than as a consequence of corticosteroid therapy. The response of the radiation changes in Case 3 was no less satisfactory than in Cases 1 and 2 and the deterioration in respiratory function was clearly related to the development of pulmonary infiltration with lymphadenoma.

Nevertheless there is also on record substantial evidence of the failure of these drugs either to exert any influence at all on radiation pneumonitis or to effect more than temporary relief, in spite of adequate dosage (Chu *et al.*, 1956), and Case 4 is a further example of this. This elderly patient had a previous history of chronic bronchitis and long-continued dust exposure and it is interesting to speculate whether these factors, as well as predisposing to the development of radiation changes, may also have affected the response of these changes to corticosteroids. Moreover it is conceivable that in some cases, perhaps as a result of individual variation in tissue response, a degree of pulmonary damage may occur which precludes reversal of the inflammatory process by corticosteroids. There was, however, a further factor, out of the realm of conjecture, which undoubtedly played a significant part in this particular patient. Considerable evidence of associated infection was observed pathologically, of a degree much in excess of that normally seen in radiation pneumonitis, and it is important to note that the organism most frequently cultured from the sputum in the latter part of the illness was *Staph. pyogenes*. The early response to treatment with prednisolone indicated the presence of some reversible change, probably tissue œdema. It now seems fairly certain that the slow deterioration of respiratory function which followed, though perhaps due primarily to cellular response to radiation injury, was contributed to materially by a widespread suppurative pneumonia and that the latter was the immediate cause of death.

The susceptibility of cases with radiation pneumonitis to develop secondary infection has long been appreciated. The danger of superinfection with the ubiquitous *Staph. pyogenes* is considerable when the patient is admitted to hospital and, in the absence of effective antibiotic control, such infection may be enhanced by the use of corticosteroids. Ideally, therefore, cases of radiation pneumonitis requiring hospitalisation should be nursed in isolation with all the precautions necessary for the prevention of cross-infection.

In the absence of definite answers to the many questions which surround the treatment of radiation pneumonitis it is reasonable to assume that the best results will occur if treatment with corticosteroids is begun early, dosage is reasonably high initially and treatment is sufficiently prolonged to allow the inflammatory reaction to subside completely. In this last respect it is of interest to note that in Cases 1 and 2 the improvement in respiratory function continued for a considerable time after stabilisation of the radiographic appear-

ances. The latter should not therefore be regarded as an index to cessation of treatment which, if premature, may lead to " rebound " phenomena (Cosgriff *et al.*, 1951; Bluestein *et al.*, 1953). The most satisfactory response in the present series was observed in a young subject with previously healthy lungs in whom the above conditions of treatment were fulfilled. In this case complete clearing of radiographic opacities and complete restoration of respiratory function was achieved by treatment extending over a period of 18 weeks.

Summary

Four cases of radiation pneumonitis treated with prednisolone are described. Two patients are alive and without respiratory symptoms 2½ years after treatment. One of these has a normal chest radiograph; the other has only slight residual pulmonary fibrosis.

Two patients died of respiratory insufficiency. Each had shown an initial response to treatment. Deterioration was due to infiltration of the lungs with lymphadenoma in one patient, and in the other uncontrolled, widespread suppurative pneumonia was the immediate cause of death.

I wish to thank Professor J. Crofton (Case 3) and Dr. I. W. B. Grant (Cases 1, 2 and 4) for permission to publish the cases and for helpful advice and criticism; Dr. N. Maclean and Dr. A. Gordon for the pathological reports; Dr. J. G. Pearson, Dr. J. Newall and Dr. K. A. Mackenzie of the Radiotherapy Department, Edinburgh, for providing details of the treatment given; Mrs. M. Beaton for performing the respiratory function tests; and Miss W. A. M. Tait for secretarial assistance.

REFERENCES

Bergmann, M., and Graham, E. A. (1951): *J. thorac. Surg.*, **22**, 549.
Bluestein, S. G., and Roemer, J. (1953): *J. med. Soc. N.J.*, **50**, 106.
Chu, F. C. H., Nickson, J. J., and Uzel, A. R. (1956): *Amer. J. Roentgenol.*, **75**, 530.
Cosgriff, S. W., and Kligerman, M. N. (1951): *Radiology*, **57**, 536.
Freidenberg, R. M., and Rubenfeld, S. (1954): *Amer. J. Roentgenol.*, **72**, 271.
Whitfield, A. G. W., Bond, W. H., and Arnott, W. M. (1954): *J. Fac. Radiol.* (*Lond.*), **6**, 12.
(1956): *Quart. J. Med.*, Vol. XXV, **97**, 67.

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PERICARDITIS FOLLOWING PNEUMONECTOMY FOR PULMONARY TUBERCULOSIS

By Ph. De Roover and A. Lacquet*

The three main causes of death after a pneumonectomy for pulmonary tuberculosis are: empyema within the empty thoracic cavity, bronchial fistula, and contralateral "spread." In addition to these heart failure, pulmonary œdema and lung insufficiency are sometimes seen.

Berard (1952) first reported 9 cases where exudative pericarditis occurred after a pneumonectomy for pulmonary tuberculosis. This condition is infrequent and a personal case induced us to review the literature on the subject and report our own case.

Case History

P.G., aged 46, had suffered since January 1954 from pulmonary tuberculosis. The right upper lobe of the lung was shrunken and contained many cavities. After prolonged treatment elsewhere, he was admitted in May 1955 to the Tuberculosis Department of the University Clinics. It was found that in addition to the many cavities in the right upper lobe, the right lower lobe was also massively involved. The lesions were active and the sputum was strongly BK-positive; the pneumonectomy had, therefore, to be postponed in spite of the fact that the left lung was healthy. In November 1956, after regular treatment with tuberculostatic agents combined with complete rest, the sedimentation was still slightly accelerated, but the sputum was BK-negative. Tomography showed that a large thin-walled cavity was present in the shrunken right upper lobe (Fig. 1).

Vital capacity: 2,190 lit.
Tiffeneau: 75%.
M.B.M.V.: 65%.

A right pneumonectomy was performed on December 13, 1956, and a large part of the pleura was removed. The lower lobe could be freed from the pericardium without opening it. The post-operative course was fairly good, but from the ninth day on the patient exhibited a high, fluctuating fever.

On the sixteenth day the patient became suddenly dyspnœic with tachypnœa, cough and sputum, but there was no hæmoptysis. Ascites and œdema developed progressively in the lower limbs. The blood pressure dropped and the circulation rate became markedly slow. The only abnormal electrocardiographic finding was a flattened T wave. The roentgenological examination revealed the presence of a hydropneumothorax on the right, so that it was difficult to evaluate the heart shadow. A few days later this appeared to be markedly enlarged and a puncture of the pericardium was performed, with the result that 400 c.c. of a seropurulent liquid were removed. The patient came immediately to life again: the blood pressure rose from 55/45 to 110/70 (Fig. 2).

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FIG. 1.—X-ray of the chest prior to operation.

FIG. 2.—X-ray of the chest taken after the operation, just before the pericardium was punctured.

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The puncture was repeated later, but the patient declined rapidly and died one month after his operation The post-mortem examination showed that he had a fibrinopurulent pericarditis which had caused an acute myocarditis.

Survey of the Literature

The occurrence of an exudative pericarditis following a pneumonectomy for pulmonary tuberculosis has been rarely mentioned in the literature. In 1952 Berard reported a case of pericarditis that occurred after a pleuro-pneumonectomy which had been performed for a purulent tuberculous pleuritis.

Our accompanying table is a summary of the cases published since 1952, including our own.

Brunner (1956) observed 2 cases in a total of 800 pneumonectomies (1, 2); Laros (1956) described in detail 4 cases (3, 4, 5, 6) which occurred in a total of 220 patients; and Berard (1956) (from 7 to 16) found 10 similar occurrences in a total of 900 resections, one of these after a resection of the right lower lobe. Björk (1956) observed 2 cases of pericarditis after 151 pulmonary resections (17, 18) and Barrie (1952) reported 3 examples (19, 20, 21) of which one occurred after a resection of the right upper lobe.

The resection was difficult in 3 cases (1, 3, 5) and the pericardium had to be opened during the operation on five occasions (8, 14, 15, 19, 20). The pneumonectomy was performed four times on the right lung and four times on the left lung, but the pleuropneumonectomy was performed only once on the right side against six times on the left side. It is probable that the pericardium is often unwittingly damaged and this is more likely to occur during a left

No.	*Sex*	*Age*	*Indications*	*Operations*
1	Male	36	Destroyed lung	Left pleuro-pneumonectomy
2	Female	29	Cavernous pulmonary tbc	Left pneumonectomy
3	Male	29	Cavernous pulmonary tbc	Right pneumonectomy
4	Female	49	Destroyed lung	Left pneumonectomy
5	Male	27	Destroyed lung	Left pneumonectomy
6	Female	25	Cavernous pulmonary tbc	Left pneumonectomy
7	Female	25	Destroyed lung	Left pleuro-pneumonectomy
8	Female	20		Left pleuro-pneumonectomy
9	Female	27		Right pneumonectomy
10	Female	37		Right pleuro-pneumonectomy
11	Female	26	Destroyed lung	Left pleuro-pneumonectomy
12	Female	25		Lobectomy of the right lower lobe
13	Female	37		Right pneumonectomy
14	Female	19		Left pleuro-pneumonectomy
15	Female	33	Destroyed lung	Right pneumonectomy
16	Male	35		Left pleuro-pneumonectomy
17			Destroyed lung	Pneumonectomy
18			Destroyed lung	Pneumonectomy
19				Pleuro-pneumonectomy
20				Pleuro-pneumonectomy
21				Resection of the right upper lobe
22	Male	46	Destroyed lung	Right pneumonectomy

Time after which the symptoms appeared	*Treatment or outcome*	*Further development*
5 days	Patient died on the 12th day	Post-mortem examination: P. fibrinosa 800 c.c. of liquid
2 months	Puncture: 400 c.c.	Pericarditis constrictiva after 9 m.
		Pericardectomy and recovery
4 months	Patient died	Pericarditis adhæsiva
Gradual decompensation	Patient died after 3 months	Pericarditis adhæsiva
		100 c.c. of a brown liquid
Gradual decompensation	Patient died after 7 months	
7 months	Patient died after 16 months	Pericarditis constrictiva
12 days	Patient died after 6 weeks	Post-mortem examination: purulent exudative pericarditis
15 days	Puncture	Patient died after 4 weeks: purulent exudative pericarditis
1 month	Puncture: serous liquid	Patient was cured
1 year	Puncture: purulent liquid	Patient was cured
3 months	Punctures: purulent liquid	Patient was cured
5 months	Puncture: serous liquid	Patient was cured
4 months		Patient was cured
15 days		Patient was cured
6 weeks	Puncture: purulent liquid	Patient was cured
Unnoticed development		Pericarditis constrictiva after 3½ years: pericardectomy
12 days	Patient died	
12 days	Patient died	
	Patient died	
	Patient died	
	Patient died	
16 days	Punctures: purulent liquid	Patient died after 32 days

pulmonary resection, particularly when a partial or complete pleurectomy has to be performed.

Discussion

Exudative pericarditis may pass unnoticed, concealed behind the diagnosis of " cardiac decompensation." It should, however, be borne in mind whenever a very long period of fever occurs after an operation.

On two occasions a pericardectomy had to be performed in the cases reported, and in one of these cases the acute episode had passed unnoticed (2, 16).

The prognosis is poor, but a single aspiration has brought about a complete relief in several cases.

The diagnosis is most difficult to establish: either the symptoms occur very rapidly during the post-operative period or they may appear later on. The picture may be very indefinite, and when there is an effusion in the treated half of the thorax it is very difficult to evaluate the roentgenological shadow of the heart. For such cases Berard (1956) recommends a radioscopy, and electrocardiographic examination may be useful.

Whatever the origin of an exudative pericarditis occurring after a pneumonectomy for pulmonary tuberculosis, damage to the pericardium in the course of the resection must be carefully avoided. In the case treated in our department where the pericardium was not opened, the diagnosis could be made only at a late stage. The punctures performed improved the patient's condition, but the secondary myocarditis aggravated the existing symptoms.

Summary

Before admitting the diagnosis of cardiac decompensation after a pneumonectomy for pulmonary tuberculosis, one should first rule out the possibility of an exudative pericarditis. Though common, this complication my occur early, but also a very long time after the operation. Pericarditis should be suspected whenever the patient has a prolonged period of high fever after the operation. The negative T wave may be absent for a long time from the ECG and the roentogram may be difficult to interpret. A post-operative effusion in the thorax can easily conceal an enlargement of the heart shadow.

The prognosis is poor but on several occasions pericardial punctures have brought about a complete cure.

REFERENCES

Barrie, (1952): *Coeur et Poumon*, 638.
Berard, M. (1956): *Lyon. Chir.*, **52,** 79.
Berard, M., Jacquemet, L. R., and Arribe-Haute, R. (1952): *Poumon*, **8,** 629.
Berard, M., Peyret, and Lacon (1956): *Poumon*, **12,** 147.
Björk, V. (1956): *J. thorac. Surg.*, **32,** 528.
Brunner, W. (1956): *Schweiz. med. Wschr.*, **86,** 1219.
Cooley, J. C., Moser, F. H., and Hedberg, G. A. (1957): *J. thorac. Surg.*, **33,** 383.
Laros, C. D. (1956): *Profschrift Groningen.*

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A RARE TYPE OF CARCINOMA OF THE TRACHEA

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The trachea forms an important segment of the lower respiratory tract, but shows a relative immunity to tumour formation. It is difficult to assess the true frequency of neoplastic disease in this site, but in a survey of reported cases of malignant disease of the trachea Ellman and Whittaker (1947) found 225 examples, while Gilbert, Mazzarella and Feit (1953), reviewing primary tracheal tumours, collected 296 benign and 250 malignant neoplasms. Clegg (1958), reporting the incidence of carcinoma of the trachea as seen at the joint Neoplastic Clinic of the Brompton and Royal Marsden Hospitals, found that in the years 1951-55 there had been 5 primary carcinomata of the trachea, compared with 1,623 proven cases of carcinoma of the bronchus.

It is the rarity of tracheal tumours, as well as the diversity of their symptomatology, that accounts for the fact that they are so often not diagnosed until necropsy. This paper describes such a case, in which bronchoscopy failed to reveal a large tracheal tumour. The histological features were unusual and have been reported elsewhere (Drury and Stirland, 1959); there has been only one previous description of a tracheal tumour with similar histology (Geschelin, 1928).

Case Report

A 68-year-old man was admitted to Central Middlesex Hospital (under the care of Dr. H. Joules) on June 28, 1957. He had worked in coal mines for twenty years, since when he had held many different jobs; latterly he had been a night watchman and had been working until about June 20.

He had had a cough, especially in winter, for at least ten years, and progressively increasing exertional dyspnœa, which latterly had restricted him to walking 200 yards slowly on level ground. About five weeks before admission his cough had increased, the sputum at first being purulent but later blood-stained. For five days his breathing had at times been noisy; it had become very difficult and interfered severely with his speech. He said that it felt as if something had got stuck in his throat but there was no history suggestive of the inhalation of a foreign body. He had smoked for many years but was vague about detailed amounts.

On examination, the patient was very dyspnœic at rest; the respiration rate was 40 per min. and at times stridor was audible. Sweating was profuse, temperature 99° F., pulse-rate 90 per min., and blood-pressure 210/95 mm. Hg. There was slight central cyanosis. The chest was emphysematous; expiration was prolonged and there were high-pitched inspiratory and low-pitched expiratory rhonchi audible throughout the lungs, but there were few crepitations. The abdomen was obese and there was a para-umbilical hernia. There was no clubbing of the fingers and no congestive failure.

Chest X-ray showed old left basal pleurisy; the lung fields were clear.

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Sputum was collected and chemotherapy started with penicillin and streptomycin intramuscularly. The sputum contained numerous pus cells and yielded a profuse growth of *H. influenzæ*, as well as a lesser growth of *Str. viridans* and Neisseria; *H. influenzæ* was sensitive to streptomycin and slightly sensitive to penicillin.

Aminophylline 0·5 g. was injected intravenously; this caused temporary improvement, but thereafter the patient's symptoms worsened and he gradually became semi-comatose. The diagnosis was thought to be either acute laryngotracheobronchitis, complicating the long-standing chronic bronchitis and emphysema, or an obstruction of the respiratory tract. There was imminent danger of suffocation and an endotracheal tube was passed. Tracheostomy was then performed under a general anæsthetic; the trachea was so heavily calcified that bone forceps were needed to make the opening, and any attempt at emergency tracheostomy in the ward would probably have failed. During the operation the larynx was inspected; it was acutely inflamed but there was no sign of neoplasm.

Post-operatively the patient's condition was satisfactory but his short, thickset neck made it difficult to keep the tracheostomy tube in place. The airway became blocked on June 29 and again on July 6; on each occasion he rapidly lost consciousness and remained in coma for several hours. Bronchoscopy had been delayed while the patient's condition appeared to be improving; on July 6 it could no longer be postponed and Mr. Maxwell Ellis examined the patient. No obstructing lesion was seen but the upper part of the trachea was never properly visualised; the bronchoscope had to be passed quickly to replace the tracheostomy tube as airway and, during withdrawal of the bronchoscope, the patient suddenly became deeply cyanosed, whereupon the anæsthetist had to reinsert the tracheostomy tube and resuscitate the patient. Severe inflammation of the mucosa of the tracheobronchial tree was noted. Supportive measures were restarted, but the patient's condition could not be sufficiently improved for bronchoscopy to be repeated and he died on July 8, after the airway had again become blocked.

At necropsy the abnormal findings were confined to the respiratory system. The larynx was acutely inflamed and œdematous, and the trachea and bronchi showed severe mucosal inflammation. Arising from the posterior wall of the trachea was a firm white broad-based tumour, measuring 3·5 × 2 × 1 cm.; the upper pole of this tumour was 2·5 cm. below the larynx and immediately opposite the tracheostomy (Fig. 1)*. The surface of the tumour was lobulated, greyish-red in colour, and showed some superficial ulceration. The lungs were œdematous and severely emphysematous, and there were some small foci of basal pneumonia. The cervical lymph nodes were enlarged and soft.

Histologically, the tumour contained two components: a fairly well-differentiated squamous carcinoma, with some areas showing prickle cells and keratin formation, and with other areas showing more anaplastic spindle-shaped cells; and a stroma which resembled a spindle-celled fibrosarcoma. Serial sections showed that the bulk of the tumour was sarcomatous, but that the carcinoma was extensive and the two components were intimately mixed. Both components of the tumour had invaded the muscular coat of the trachea, but the cervical lymph nodes were free from metastasis. The carcinomatous component formed a definite entity, but Drury and Stirland (1959) could not

* The figure number refers to Plate LI.

determine whether the sarcomatous component was a genuine sarcoma or a benign exuberant stromal reaction.

Discussion

Reviews of the diverse symptomatology, physical signs and differential diagnosis of tracheal tumours accumulate (*e.g.* Jackson and Jackson, 1938; Ellman and Whittaker, 1947; Moersch, Clagett and Ellis, 1954), and, therefore, only selected features of this case will be discussed. In retrospect, the correct diagnosis was very probable on clinical grounds, and the rarity of tracheal tumours cannot be accounted sufficient reason for not having investigated the patient more intensively. Too much importance was attributed to the history of chronic respiratory insufficiency. More note should have been taken of the combined facts that he had obstructive dyspnœa with stridor, a temperature that was barely elevated, and a chest radiograph that revealed nothing to account for his recent symptoms. As Ellman and Whittaker (1947) wrote: ". . . A normal chest radiograph in cases of respiratory obstruction suggests a tracheal or mediastinal lesion."

Reliance was placed upon bronchoscopy to exclude an endotracheal tumour, but difficulties with the airway during this investigation prevented an adequate view of the critical part in the trachea. With the tracheostomy tube in place the bronchoscopist could not see the tumour, which would then have been compressed against the posterior wall of the trachea, and when the bronchoscope was withdrawn over the tumour the airway immediately became obstructed. A lateral X-ray of the neck might well have revealed the diagnosis (Andren, 1937). If it had been recognized, local resection of the tumour might have benefited the patient, as the necropsy demonstrated that it had not extended beyond the trachea, but Barrett (1958) stressed the generally poor prognosis carried by malignant disease of the trachea.

Geschelin (1928) described a tracheal tumour with macroscopic and histological features very similar to those of the present case. His 68-year-old patient gave a three months' history of dyspnœa and weight loss, and presented with marked stridor. The tumour arose from the lateral wall of the upper trachea and was visible on laryngoscopy; tracheostomy was performed followed by a local resection, but the patient died seven days later from bronchopneumonia. Histologically the tumour contained an epithelial carcinoma, which was sharply demarcated from a fibrosarcomatous stroma, and Geschelin concluded that it was a carcinosarcoma.

Mixed tumours of epithelial and mesenchymal origin (excluding teratomata) are rare, and a diagnosis of carcinosarcoma should not readily be made. Saphir and Vass (1938) reviewed 153 so-called carcinosarcomata and concluded that only three or four could be regarded as true examples; they considered that most " carcinosarcomata " were neither " collision " nor combination tumours but primary carcinomata, and they suggested that in some cases the connective tissue element might be caused by inflammatory reaction, particularly in tumours of organs where infection was likely to occur (*e.g.* oral cavity, uterus). Saphir and Vass (1938) did not assess the tumour described by

Geschelin (1928). Bergmann, Ackerman and Kemler (1951) reconsidered the criteria necessary for a diagnosis of carcinosarcoma and expressed doubt as to whether Saphir and Vass (1938) were justified in rejecting such a high proportion of cases. Drury and Stirland (1959) accept the tumour described by Geschelin (1928) as a carcinosarcoma, and it is possible that the case reported here is the second recorded example of a tracheal carcinosarcoma.

In 1929 deaths from carcinoma of the lung and of the larynx, in males, were about equal in number; there has since been a progressive increase in deaths from the former, whereas deaths from the latter have decreased (Maxwell, 1955; Kennaway, 1957). Carcinoma of the trachea has not been reported to be increasing, but both the larynx and trachea are exposed to cigarette smoke, a factor which is probably closely related to the increased incidence of bronchogenic carcinoma (Medical Research Council, 1957). Maxwell (1955) believes that the main contact of an inhaled irritant with the respiratory epithelium must be in the larynx, and Moersch *et al.* (1954) state that the trachea is exposed to dangers from inhalation that are as great as in the bronchi and larynx.

It may, however, be untrue to assume that the main impact of inspired carcinogens is upon the larynx and trachea; this assumption takes no account of the many factors which can affect the stability or deposition of inspired dusts, mists and vapours (Drinker and Hatch, 1936). Drinker and his colleagues showed that in animals deposition of fumes of ferric oxide took place principally in the alveoli, and that the trachea usually did not contain demonstrable amounts of iron (Titus, Warren and Drinker, 1935); in another experiment, sulphuric acid mist produced marked pulmonary damage, but the larynx and trachea were normal (Amdur, Schulz and Drinker, 1952). Tobacco smoke is composed mainly of microscopic oily droplets held in suspension in air; these droplets may show a lesser tendency to aggregate and be deposited during their rapid and turbulent passage through the larynx and trachea than in the bronchial and alveolar network, where other factors such as humidification and the progressive cooling of the smoke may assume importance. This may explain the relative rarity of laryngeal and tracheal carcinoma, on the assumption that the most probable cause of bronchial carcinoma, a component of cigarette smoke, is failing to make contact with the epithelium in these sites. Other reasons, some susceptible to experimental testing, have been advanced to explain these differences in incidence (Moersch *et al.*, 1954; Peacock, 1958).

Summary

The case history is presented of a patient who died from the effects of a large tracheal tumour. This tumour is possibly the second recorded case of tracheal carcinosarcoma. The rarity of laryngeal and tracheal carcinoma is discussed in relation to the increasing incidence of bronchogenic carcinoma.

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REFERENCES

AMDUR, M. O., SCHULZ, R. Z., and DRINKER, P. (1952): *Amer. med. Ass. Arch. indust. Hyg.*, **5**, 318.

ANDREN, G. (1937): *Acta radiol. (Stockh.)*, **18**, 249.

BARRETT, N. R. (1958): In "Cancer," vol. 4, p. 301. Ed. by R. W. Raven. London: Butterworth.

BERGMANN, M., ACKERMAN, L. V., and KEMLER, R. L. (1951): *Cancer (N.Y.)*, **4**, 919.

CLEGG, J. W. (1958): In "Cancer," vol. 2, p. 563. Ed. by R. W. Raven. London: Butterworth.

DRINKER, P., and HATCH, T. (1936): "Industrial Dust." New York: McGraw-Hill Inc.

DRURY, R. A. B., and STIRLAND, R. M. (1959): *J. Path. Bact.*, **77**, 543.

ELLMAN, P., and WHITTAKER, H. (1947): *Thorax*, **2**, 153.

GESCHELIN, A. (1928): *Z. Laryng. Rhinol. Otol.*, **16**, 402.

GILBERT, J. G., MAZZARELLA, L. A., and FEIT, L. J. (1953): *Arch. Otolaryng. (Chicago)*, **58**, 1.

JACKSON, C., and JACKSON, C. L. (1938): *Amer. J. Surg.*, **42**, 275.

KENNAWAY, E. (1957): *Brit. med. J.*, **1**, 299.

MAXWELL, J. (1955): *Lancet*, **1**, 193.

MEDICAL RESEARCH COUNCIL (1957): *Brit. med. J.*, **1**, 1523.

MOERSCH, H. J., CLAGETT, O. T., and ELLIS, F. H. (1954): *Med. Clin. N. Amer.*, **38**, 1091.

PEACOCK, P. R. (1958): In "Cancer," vol. 1, part 1, p. 32. Ed. by R. W. Raven. London: Butterworth.

SAPHIR, O., and VASS, A. (1938): *Amer. J. Cancer*, **33**, 331.

TITUS, A. C., WARREN, H., and DRINKER, P. (1935): *J. industr. Hyg.*, **17**, 121.

PLATE LI

FIG. 1.—Lateral view of the larynx and trachea showing the tumour and the site of the tracheostomy.

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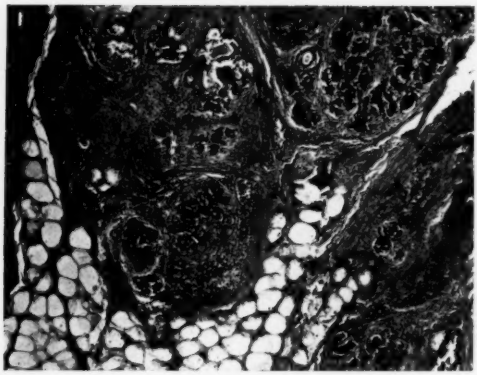


FIG. 1.—Pancreas: The acini are small and there is widespread fibrosis. Adipose tissue is present between the lobules.

H. and E. ×40.

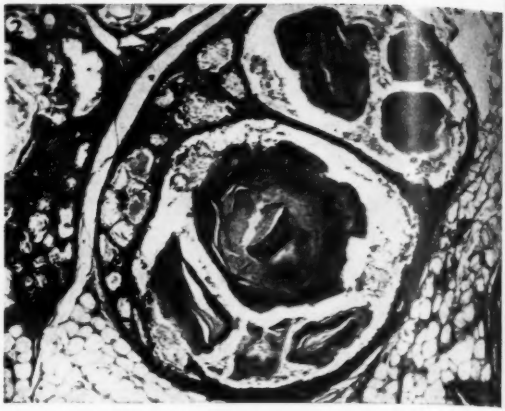


FIG. 2.—Pancreas: This shows a dilated duct which contains several large acidophilic concretions.

H. and E. ×40.

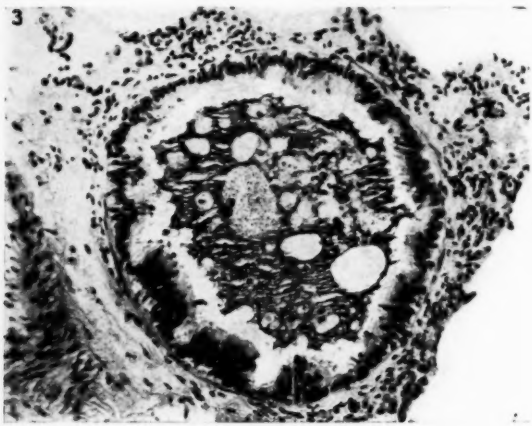


FIG. 3 (*left*).—Lung: This section of the upper lobe of the right lung shows a small bronchus filled with mucus.

Periodic Schiff and Haemalum. ×185.

FIG. 4 (*below*).—Bronchus: This shows dilation of the glands and ducts in the submucosa. The surface is ulcerated and there is a widespread infiltration with inflammatory cells.

Periodic Schiff and Haemalum. ×25.

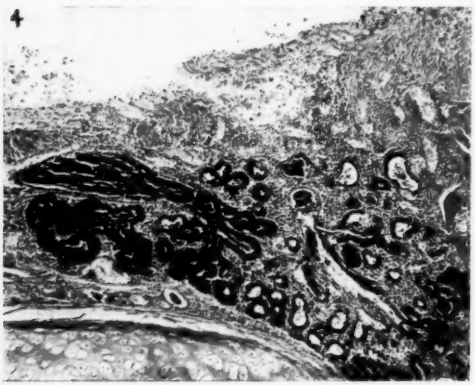
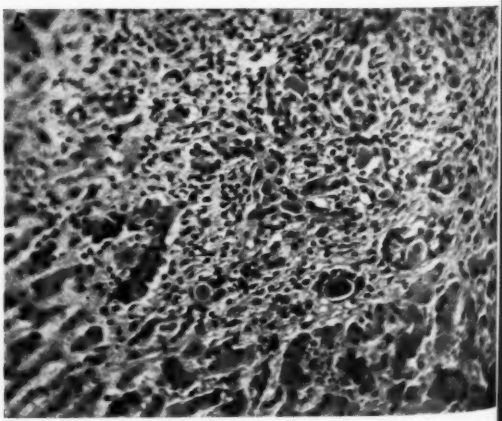


FIG. 5 (*below*).—Liver: This shows fibrosis around the portal tract. Several ducts are seen dilated with secretion.

H. and E. ×185.



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FIBROCYSTIC DISEASE OF THE PANCREAS PRESENTING AS BRONCHIECTASIS IN AN ADOLESCENT

By A. W. Lees and G. B. S. Roberts

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Until recently it was believed that patients suffering from fibrocystic disease of the pancreas did not survive early childhood. The following case history is a reminder that this view is no longer tenable, and it also illustrates that chronic respiratory infection may be the only obvious manifestation of the disease.

Case Report

A girl aged 14 years was admitted to Ruchill Hospital on 29.6.56 because of an acute exacerbation of chronic respiratory infection. According to her mother she had been troubled with a productive cough since early childhood and had been treated in various hospitals for attacks of pneumonia.

The patient was a thin, pale, apyrexial girl with slightly clubbed fingers. She was not dyspnœic at rest. There was no cyanosis, jaundice or œdema. The chest expansion was poor and there were numerous crepitations at both bases. A chest film showed generalised catarrhal changes. No abnormality was detected in the cardiovascular or nervous systems. The liver, spleen and kidneys were not palpable and examination of the blood and urine showed no abnormality. The patient had never menstruated. The sputum was purulent and on admission 4 oz. were produced in 24 hours; repeated cultures were negative for *M. tuberculosis*. The patient responded well to treatment with tetracycline 1 g. daily, postural drainage and breathing exercises. Her general condition improved greatly. The daily output of sputum fell to about 1 oz. and she was able to get up and about. Bronchography showed slight cylindrical bronchiectasis in all the pulmonary segments. She was discharged from hospital on 21.9.56.

After discharge from hospital the patient attended the Out-patient Department for periodic check. She continued to carry out her breathing exercises and postural drainage at home and remained in fairly good health. Her daily output of sputum averaged about 1 oz., and although she was breathless on hills she was able to keep up with people of her own age on level ground. She took up work as a typist and, except for a fortnight's absence due to a cold, she was in continuous employment until 2.12.57, when she had to be readmitted to hospital because of breathlessness, lassitude and a persistent cough, associated with the production of abundant purulent sputum.

On admission the patient was dyspnœic and slightly cyanosed. Rhonchi and crepitations were present all over the lung fields and a chest film showed widespread areas of collapse. She brought up 6 oz. of sputum in 24 hours. Her condition improved in response to tetracycline therapy supplemented with postural drainage. She still coughed up 2 to 3 oz. of sputum per day, however, and became dyspnœic with mild exercise. On 12.12.57 she became cyanosed, acutely dyspnœic and had difficulty in bringing up sputum. Rhonchi were heard all over the lung fields. She was given oxygen, put in a steam tent, and

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treated with chloramphenicol and erythromycin, as examination of sputum showed that penicillin resistant staphylococci were present. This treatment produced rapid improvement and the patient was subsequently able to get up, although she was breathless on mild exertion. On 21.3.58, however, the patient again became cyanosed and acutely dyspnœic and her condition slowly deteriorated in spite of oxygen, steam and antibiotic therapy. She died on 27.3.58.

Post-mortem Examination

The body is that of a rather thin, poorly nourished girl aged about 16 years. There is clubbing of the fingers and the face is cyanosed. No distension of the abdomen is noted.

The mouth and pharynx show no gross abnormality. The trachea and bronchi contain a large amount of very tenacious muco-purulent secretion and the main divisions of the bronchi appear to be completely filled with this material. The mucosa lining the respiratory passages shows severe inflammatory congestion. The lungs lie free and the pleural cavities show no gross abnormality. The lungs are very voluminous owing to extensive emphysema. Wedge-shaped areas of collapse are present, particularly in the posterior portions of the lower lobes. Section of the lungs reveals that many bronchi are dilated and are filled with thick creamy pus, and in places infection has spread into the lung substance, and has resulted in the formation of lung abscesses. Areas of collapse are seen around many of the bronchi and in the lower lobes there is some broncho-pneumonia. Widespread emphysema is present in the lung alveoli between the areas of collapse, but no gross fibrosis is seen. The heart is moderately enlarged, due to hypertrophy of the right ventricle. No other muscular and no valvular abnormality is present. The myocardium is normal and no congenital malformation is present.

Peritoneum, omentum and mesentery are normal and the alimentary tract shows no features of note. The liver is normal in size, but the surface is irregular and section shows a widespread fine fibrosis. The gall bladder is small in size and is filled with clear viscid mucus. The pancreas is normal in size and shape. On section the organ is fibrosed and is seen to contain a considerable amount of fat. Multiple small cysts are seen, especially in the head and body. The main duct is dilated and contains clear mucus. The spleen appears normal and the kidneys, ureters and bladder show no features of note.

Histology

The pancreas (Fig. 1)* contains a large amount of fat intersected by strands of dense fibrous tissue. The pancreatic exocrine tissue has largely disappeared and only a few small groups of acini are seen. These acini are small in size and are usually surrounded by fibrous tissue. None of the acinar cells is fully developed and none contains cymogen granules. The most striking feature in the pancreas is the large number of cysts which are present. These cysts are lined by a columnar mucus-secreting epithelium and frequently contain acidophilic concretions (Fig. 2).

The lung shows extensive purulent bronchitis with bronchiectasis in the lower lobes. There is widespread emphysema and a few segments of collapse of the lung are noted. Many of the smaller bronchi in the upper lobes are filled with mucus (Fig. 3), and the main bronchi show evidence of excessive

* The figure numbers in the text refer to Plate LII.

secretion of mucus (Fig. 4). The Brünner's glands in the duodenum are greatly dilated and contain an excessive amount of mucus. The liver (Fig. 5) shows areas of periportal fibrosis, and in this region there are aggregations of an orange-brown pigment which does not appear to be either bile or mucus.

Discussion

In the earlier reports of fibrocystic disease of the pancreas (Fanconi *et al.*, 1936; Andersen, 1938) two salient features are described—gastro-intestinal disturbance due to deficiency of external pancreatic secretions, and chronic infection of the respiratory tract. These disorders are due to blockage of the pancreatic ducts and of the smaller bronchi by abnormally viscid mucus. It is now known that fibrocystic disease of the pancreas is a more generalised disease than was originally supposed: in addition to pancreatic and respiratory involvement the salt content of the sweat may be increased (di Sant' Agnese *et al.*, 1953a), intestinal mucus may be abnormally viscid (Schwachman *et al.*, 1955), the production of saliva may be unusually copious (di Sant' Agnese, 1956), and areas of biliary cirrhosis may develop in the liver (Andersen, 1938; Farber, 1944), sometimes giving rise to portal hypertension (di Sant' Agnese, 1956). Increased salt content of the sweat, present in at least 99 per cent. of cases (di Sant' Agnese, 1956), is the most constant manifestation of the disease, and sweat analysis is therefore the most reliable diagnostic test. Fibrocystic disease of the pancreas is hereditary (Andersen, 1949), and investigation of relatives of florid cases has shown that the characteristic alteration in sweat electrolytes may be the only manifestation of the disease; or there may be a positive sweat test and chronic respiratory infection but no evidence of pancreatic dysfunction (di Sant' Agnese *et al.*, 1953b; Schwachman *et al.*, 1956).

In the present case histological examination of the pancreas postmortem showed areas of fibrocystic disease and, had tests for steatorrhœa and tryptic activity of duodenal juice been carried out during life, they might have revealed evidence of diminished pancreatic function. Certainly pancreatic insufficiency was not obvious clinically, for diarrhœa or the passage of bulky or offensive stools was not noted at home or in the various hospitals in which the patient had been treated for exacerbations of respiratory infection.

About 10 per cent. of patients with fibrocystic disease of the pancreas die shortly after birth as a result of meconium ileus (Andersen, 1938), but if this first hurdle is surmounted prognosis depends chiefly on the degree of respiratory involvement. The total number of deaths in a series of 325 cases observed by di Sant' Agnese (1956) was 145, and chronic respiratory disease accounted for 130 (90%) of them. Seven (2%) of his patients developed portal hypertension and in some this complication dominated the clinical picture and determined the fate of the patient. Pancreatic insufficiency, though influencing nutrition and growth, played a relatively small role as regards survival.

The outlook in fibrocystic disease of the pancreas is better than earlier experience suggested, partly because of improved therapy for respiratory infection, and partly because milder cases are now being recognised. Twenty-four (7%) of the patients in di Sant' Agnese's (1956) study were aged more

than 10 years and one patient was still alive at the age of 19 years. This improvement in prognosis, which has been more widely reported in the U.S.A. than in this country, is worth bearing in mind, as recognition that chronic respiratory infection is a manifestation of fibrocystic disease of the pancreas may be of more than academic interest. Although there is generalised involvement of the mucous glands of the respiratory tract there may be localised bronchial blockage with resultant atelectatic bronchiectasis. Kulczycki *et al.* (1957) report the surgical excision of bronchiectatic lobes in six children with fibrocystic disease of the pancreas: as the correct diagnosis was not established until some time after operation in two of them, they suggest that sweat analysis should be carried out in all children in whom resection for bronchiectasis is contemplated, as the result may well influence the decision to operate. Even in young adults this would seem to be a reasonable precaution.

Summary

An account is given of a female who died at the age of 16 years from an exacerbation of chronic respiratory infection. During life there had been no indication of gastro-intestinal disturbance but histological examination post-mortem revealed lesions characteristic of fibrocystic disease of the pancreas in the lungs, pancreas and liver. Attention is drawn to the possibility of failing to recognise that fibrocystic disease of the pancreas is the underlying cause of chronic respiratory infection, especially in an older child or adult who has no gastro-intestinal symptoms.

REFERENCES

Andersen, D. H. (1938): *Amer. J. Dis. Child.*, **56,** 344.
(1949): *Proc. roy. Soc. Med.*, **42,** 25.
di Sant' Agnese, P. A. (1956): *J. Amer. Med. Ass.*, **160,** 846.
di Sant' Agnese, P. A., Darling, R. C., Perera, G. A., and Shea, E. (1953a): *Pediatrics*, **12,** 549.
di Sant' Agnese, P. A., Darling, R. C., Perera, G. A., and Shea, E. (1953b): *Amer. J. Med.*, **15,** 777.
Fanconi, G., Uelinger, E., and Knauer, C. (1936): *Wien. med. Wschr.*, **86,** 753.
Farber, S. (1944): *Arch. Path.*, **37,** 238.
Kulczycki, L. L., Craig, J. M., and Schwachman, H. (1957): *New Engl. J. Med.*, **257,** 203.
Schwachman, H., Leubner, H., and Catzel, P. (1955): *Mucoviscidosis, Advances in Pediatrics*, **7,** 249.
Schwachman, H., Dooley, R. R., Guilmette, F., Patterson, P. R., Weil, C., and Leubner, H. (1956): *Amer. J. Dis. Child.*, **92,** 347.

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EDWARD VI: A ROYAL CONSUMPTIVE

By Sir Arthur MacNalty, K.C.B.

Edward VI, the son of Henry VIII and Jane Seymour, was born at Hampton Court Palace on October 12, 1537. It was a prolonged and difficult labour, and it is believed that Dr. George Owen delivered the Queen by Cæsarean section. King Henry was overjoyed, but Queen Jane died from puerperal sepsis twelve days after the birth.

Family History. The Tudors appear to have had an hereditary predisposition to pulmonary tuberculosis. Henry VIII's robust constitution resisted the tubercle bacillus, but Henry VII, Edward's grandfather, had probably tuberculosis of the joints, associated with the disease " which wasted his lungs " (Bacon). He died at the age of 52 from consumption (Polydore Vergil). Prince Arthur, the elder son of Henry VII and Elizabeth of York, was born in 1486 and died in 1502. He was delicate from birth, thin and subject to repeated attacks of fever and coughing. It seems probable that he was infected with tuberculosis by his father, although the actual cause of his death at Ludlow was the sweating sickness, prevalent in the West Country in 1502. Catherine of Aragon, whom Arthur had married four months previously, was attacked by the disease and recovered, but Prince Arthur's frame, debilitated by consumption, lacked the resistance to cope with the epidemic. Henry, Duke of Richmond, a natural son of Henry VIII by Elizabeth Blount, one of the ladies-in-waiting to Queen Catherine, was born in 1519. He greatly resembled his royal sire, and married the sister of his friend, the ill-fated Earl of Surrey. King Henry was warmly attached to his son and at one time contemplated making him heir to the throne. On July 8, 1536, it was reported that " the King's bastard son . . . cannot, according to the prognostications of his physicians, live many months, having been pronounced to be in a state of rapid consumption." He died on July 23,1536, at the age of 17.

Childhood and Education

Prince Edward appears to have been a healthy normal child. Henry VIII gave minute instructions for his upbringing in which hygienic care much in advance of the times figured. Precautions against murder and infection were set out in the King's own hand. Lady Bryan was chiefly responsible for Edward's infantile upbringing. For medical care Dr. George Owen was directly responsible to the King. At four years of age Edward began his education, but soon afterwards while at Hampton Court fell sick of a quartan fever (malaria). The illness was severe, but by December 1541 he was better and completed his convalescence at Ashridge, with frequent visits from Dr. Butts, the King's physician. At six years his education was undertaken by Dr. Richard Cox, Provost of Eton and Canon of Westminster. His other tutors were Vannes, Roger Ascham and Sir Anthony Cooke; and he partly shared the studies of

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his half-sister Elizabeth. The course of study, the contemporary historian John Heywood tells us, was hard. With daylight Edward and Elizabeth were at their books, the first hours being devoted to their religious exercises and the study of the Scriptures. "The rest of the forenoon, breakfast alone excepted, they were instructed in languages (Latin, Greek, French, Italian and Spanish) and science (mathematics) and moral learning." In the afternoon Edward studied music, dancing and outdoor sports and games. He preferred tilting and running at the ring to hawking and tennis. He was a clever and industrious boy, but not a brilliant one. In 1544 Henry VIII, on the advice of Dr. Butts, made Sir John Cheke, a fellow of St. John's College, Cambridge, his son's chief tutor. Cheke was a learned and inspiring scholar, and his influence guided the prince from his seventh to his fourteenth year. The intensive system of education made Edward's outlook rigid and unimaginative, but he was less of an intellectual prig than has been supposed, having much of the Tudor spirit and energy and being popular with his subjects.

The Boy King

In 1547 Henry VIII died and Edward became King of England. Edward Seymour, Earl of Hertford (later Duke of Somerset), was made Protector, allied himself with the Reformed party and invaded Scotland to enforce a marriage between Edward and Mary, Queen of Scots. At Pinkie Cleugh the Scots were defeated, but the child-queen was sent to France and betrothed to the Dauphin. Edward wished to unite England and Scotland by marrying Mary. When he entertained the Queen-Regent, Mary of Guise, on her return journey from France to Scotland in 1551, he personally approached her in vain on the subject. Thereafter, tentative negotiations were begun with France for the King to marry Princess Elizabeth, Henry II's daughter. By this time Somerset had fallen and was executed in 1552. John Dudley, Earl of Warwick, had seized the reins of power and became Duke of Northumberland. In matters of state and in advancing the Reformation Edward was naturally controlled first by Somerset and afterwards by Northumberland.

In 1551 the last severe outbreak of sweating sickness occurred in England. This was described by John Caius in a treatise entitled: *A Boke or Conseil against the Disease Commonly called the Sweate or Sweating Sickness* (1552). In April rumours that Edward had died from the disease made it necessary for him to ride in full armour through London and to participate in a public military review. His close friend, the young Duke of Suffolk, died from sweating sickness in July, but Edward escaped the infection. Cheke had the disease and recovered.

Illness and Death

Although reported by the French and Spanish ambassadors as "delicate, thin and weakly," probably for political reasons, the boy king appears to have enjoyed good health until April 1552, when he wrote in his journal: "I fell sike of the mesels and the small pokkes." The two diseases measles and smallpox were often confused, and he probably had a severe attack of measles.

He had outgrown his strength, becoming tall, and the combined pressure of his education, state affairs and anxiety about the maintenance of the Reformed religion sapped his power of resistance against pulmonary tuberculosis to which the attack of measles predisposed. He suffered from fever, night-sweats, " a racking cough " with sputum occasionally blood-stained.

Edward made a royal progress in Sussex, Hampshire and Wiltshire in the autumn of 1552. He hunted most of the day and looked so frail that general pity was felt for him. Miss Hester Chapman in her authoritative *Life of Edward VI* notes that Girolamo Cardano, a celebrated Italian doctor and astrologer who had cured the Archbishop of St. Andrews of asthma, was summoned to visit the King. His secret opinion was that Edward showed " the mark of death in his face that was to come so soon." He liked Edward and got permission to dedicate his book, *De Varietate Rerum*, to him. Cardano did not dare to tell Northumberland and the Council his true opinion, but produced a false horoscope of Edward, warned against over-fatigue, and departed in safety to Italy. Edward gave him a fee of a hundred gold crowns.

The King's disease progressed, although at intervals he rallied. In May, 1553, it was officially announced that he was only a little sick and overtired. In reality Edward's cough was harsh and continuous, his fever very high, his abdomen swollen and at times he was delirious. His physicians plied him with nauseous drugs and stimulants; for Northumberland in order to mature his plans to secure the succession of Lady Jane Grey, his daughter-in-law, desired them to keep the King alive as long as possible. Septic infection from neglected bed-sores supervened and caused the patient much agony. Possibly, the King had also Raynaud's disease, for his gangrenous fingers and toes fell off. He prayed for death but the physicians would not let him die in peace. William Cecil, who read their reports to Northumberland, wrote to a sick friend: " God deliver you from the physicians." In June crowds assembled round Greenwich Palace, and Northumberland had the dying and emaciated boy lifted out of bed and held up at the window to show that he was still alive.

Dr. Owen and Dr. Wendy told Northumberland that the King was sinking, whereupon the angry Duke dismissed them and called in his own doctor and an Oxford physician (probably John Warner, M.D.Oxon., F.R.C.P., the first Regius Professor of Physic), together with a female quack or " wise woman." This wretched woman was given sole charge of Edward, and hastened his death by the administration of a nostrum which seems to have contained arsenic. Round his sick bed wrangled Northumberland and members of the Council about the succession. When July came and the end was near, the " wise woman " was removed and the royal physicians recalled. On July 6 the King died, aged fifteen years and nine months. His last words were: " Lord have mercy upon me—take my spirit."

REFERENCES

CHAPMAN, HESTER W. (1958): " The Last Tudor King: A Study of Edward VI." London: Jonathan Cape.

FROUDE, J. A. (1856-70): " History of England from the Fall of Wolsey to the Death of Elizabeth (Edward VI)." London.

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DOMICILIARY TREATMENT OF PULMONARY TUBERCULOSIS IN A RURAL AREA

A PRELIMINARY REPORT ON 7,858 CASES TREATED IN THE TRANSKEIAN TERRITORIES

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The Transkei is an area in the north-eastern Cape Province, 16,554 square miles in extent, and mostly undulating grassland country in nature. The climate varies from a subtropical one along the coast to one of extremes of heat and cold at the higher inland altitudes. The average summer rainfall is 30 inches.

The population comprises 1·6 million Bantu and 18,000 Europeans. The Europeans live in 28 villages with populations varying between 150 and 600; the distance between these villages varies from 20 to 50 miles.

The Bantu live a rural life under the tribal system: their huts—single wattle and daub structures with thatched roofs and clay floors—are fairly evenly distributed over the entire area.

An estimated 240,000 Bantu males are continually away from the area, working in mines and industrial centres: there is thus a continuous flow of labourers to and from the cities. The majority of Bantu are partly dependent upon relatives employed in urban areas.

The main crop is maize: cattle are still regarded as a measure of wealth rather than as a source of food.

The Transkei is traversed by 1,150 miles of main road and 5,000 miles of subsidiary roads: large stretches of the latter are, for days on end, impassable during the rainy seasons.

Domiciliary Treatment

Domiciliary treatment of tuberculosis was instituted in September 1955: at that time the estimated number with active pulmonary tuberculosis was 25,000 to 30,000 (Wiles and Rabie, 1955).

About 500 beds were available for patients with pulmonary tuberculosis.

The assistance of 30 part-time district surgeons, eleven Mission Hospitals and one Health Centre was enlisted. By utilising the clinics thus available, domiciliary treatment could be carried out at some 300 points in the area.

Twelve X-ray machines were scattered throughout the area, and it is estimated that 75 per cent. of clinical diagnoses were radiologically confirmed.

The standard treatment consisted of one weekly injection of 2 g. of streptomycin and 400 mg. of INAH daily. In April 1957 the dose of INAH was doubled and fixed at 10 to 12 mg./kilo/day.

Of the cases diagnosed, roughly 80 per cent. live within a radius of 5 miles

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from the nearest treatment point. Patients walk to their centres: only very occasionally is use made of transport—by sledge or on horseback.

After the scheme had been in operation for two years the gathering of certain information was attempted: the total diagnosed now numbered 16,000.

In compiling this information the districts concerned were limited to those where the original X-rays of cases on treatment were reasonably available. Districts excluded were those without X-ray facilities or those where the X-ray filing systems precluded the finding of required plates.

The selected districts were visited by a mobile X-ray unit and its staff (a European driver-operator and a Bantu clerk); each patient present was X-rayed and also furnished a sputum specimen. In addition, the attendance card or register for each patient was scrutinised. The two mobile X-ray units thus visited 203 different treatment points.

The information collected is reflected in Tables 1 to 13.

TABLE 1.—DISEASE CLASSIFICATION OF 7,858 CASES OF PULMONARY TUBERCULOSIS DIAGNOSED OVER A TWO-YEAR PERIOD. THE DISEASE GROUPS ARE DIVIDED IN SEX AND AGE GROUPS

Disease classif.	-5 *y.*		6-15 *y.*		16-34 *y.*		35 *y. and over*		*Whole group*		
	M.	*F.*	*M.*	*F.*	*M.*	*F.*	*M.*	*F.*	*M.*	*F.*	*M.&F.*
Min.	0·8	1·7	5·6	5·8	8·8	10·7	8·2	8·4	6·6	7·5	7·2
Mod.	20·3	18·5	13·8	23·3	32·8	28·0	32·8	37·6	29·8	30·2	30·2
Adv.	14·0	15·3	26·1	22·0	38·1	37·4	39·0	40·5	34·2	34·1	34·0
Gr. des.	4·5	2·8	9·7	7·5	14·6	19·6	13·3	9·7	10·6	10·7	10·6
Prim.	60·1	60·3	44·0	39·7	1·5	1·2	0·6	0·4	14·6	14·8	14·5
Pl. eff.	0·3	0·4	0·6	1·7	4·2	3·1	6·1	3·4	4·2	2·7	3·5
Size of groups ..	627	629	268	399	621	1,023	2,142	2,082	3,658	4,200	7,858
	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Age groups as % of total	1,323		667		1,644		4,224		7,858		
	16·9%		8·5%		21·1%		53·4%		100%		
Recent disease in adult group					53·3	56·7	49·3	53·0	50·2	55·6	52·5
Fibrotic disease in adult group					46·7	43·3	50·7	47·0	49·8	44·4	47·5
Size of groups					630	979	2,046	2,020	2,676	2,999	5,675
					100%	100%	100%	100%	100%	100%	100%

The figures regarding X-ray improvement are not based on the total number of patients in any particular group—in a considerable number the progress remained unknown for reasons indicated below.

At times inclement weather made it impossible to visit certain points on the day specified: patients attending such points could therefore not be X-rayed. Bad roads, breakdown of the X-ray unit and poor organisation in some districts were additional reasons why follow-up X-rays could not always be done.

Great difficulty was also encountered in the spelling of Bantu names: the use of alternative names by the same patient on different occasions resulted in the loss of a large number of follow-up X-rays.

Finally there were those cases who, for no known reason, failed to turn up on the occasion the X-ray unit visited their treatment point. This group possibly stayed away for some reason related to X-ray clearing—such reason, however, cannot be envisaged. (See Tables 6 and 7.)

This aspect of the investigation, at first sight, appeared unsatisfactory. After careful consideration, however, and also with the expressed approval of the Department's statistical consultant, it was decided that the figures obtained are probably significant.

TABLE 2.—DISEASE CLASSIFICATION OF A FEW SUB-GROUPS

Disease Classif.	*Cases diagnosed over 6-month period two years ago*	*Cases diagnosed during past 6-month period*	*Cases diagnosed but never reported for treatment*	*Cases diagnosed by Mobile Unit (Suspects)*
Minimal	7·4%	8·1%	8·3%	10·3%
Moderate	26·8%	32·7%	30·0%	42·1%
Advanced	36·6%	33·4%	28·7%	35·5%
Gross destruction ..	15·0%	7·3%	10·7%	5·1%
Primary P.T.B. ..	10·7%	14·8%	19·5%	2·7%
Pleural effusion ..	3·5%	3·7%	2·8%	4·3%
Number of cases ..	1,551 100%	2,599 100%	515 100%	647 100%
Recent dis. ..	49·5%	58·8%	55·0%	58·5%
Fibrous dis. ..	50·5%	41·2%	45·0%	41·5%
Number of cases ..	1,346 100%	2,131 100%	402 100%	608 100%

DISEASE CLASSIFICATION

(*a*) *Disease Classification of* 7,858 *Cases of Pulmonary Tuberculosis diagnosed during a Two-year Period* (*Table* 1)

In the age group " 5 years and younger," about 40 per cent. have more than a primary complex.

The age group " 6 to 15 years," as is expected, is a small group. Here, too, 33 per cent. have advanced or grossly destructive lesions.

In the " 16 to 34 years " group the females predominate: 62 per cent. to the 38 per cent. males. This is also the group having the highest percentage of grossly destructive lesions; furthermore the percentage among the females is higher than among the males. This is doubtless explained by the fact that this age group covers the child-bearing period of the female—the period associated with greatly increased physiological stresses.

In the group " 35 years and older," which forms 53 per cent. of cases on treatment, the cases with advanced lesions form 51 per cent.

There appears to be no great difference in the stage of advancement of the disease at the time of diagnosis between the two adult age groups, or between males and females.

TABLE 3A.—ATTENDANCE AND PERCENTAGE NOT COMPLETING TREATMENT

Attendance during first six months of treatment

Dis. classif.	*Class 1 att.*	*Class 2 att.*	*Class 3 att.*	*Not compltg.*	*No. cases*	
Minimal	54·0%	23·3%	9·7%	13·0%	300	100%
Moderate	52·8%	22·8%	9·7%	14·7%	1,288	100%
Advanced	51·8%	22·7%	9·8%	15·7%	1,569	100%
Gross destr.	52·2%	19·7%	10·8%	17·3%	522	100%
Primary	38·4%	24·9%	13·6%	23·1%	652	100%
Pleural eff.	45·1%	26·2%	11·7%	17·0%	153	100%
Recent dis.	50·3%	23·6%	10·7%	15·4%	2,061	100%
Fibrotic dis.	54·8%	21·5%	8·9%	14·8%	1,649	100%
Unclassif.	45·5%	18·1%	10·1%	26·3%	2,729	100%
Whole group ..	48·5%	20·6%	10·6%	20·3%	7,213	100%
Size of group ..	3,499	1,484	753	1,467	7,213	

Attendance during second six months of treatment

	Class 1 att.	*Class 2 att.*	*Class 3 att.*	*Not cmpltg.*	*No. cases*	
Minimal	49·3%	27·0%	13·0%	10·8%	173	100%
Moderate	46·7%	26·6%	16·0%	10·7%	638	100%
Advanced	42·5%	28·5%	18·3%	10·7%	857	100%
Gross destr.	46·0%	22·2%	14·6%	17·2%	308	100%
Primary	32·1%	26·7%	22·1%	19·1%	262	100%
Pleural eff.	40·3%	27·3%	26·0%	6·4%	77	100%
Recent dis.	42·5%	29·2%	17·3%	11·0%	1,063	100%
Fibrotic dis.	47·8%	24·7%	15·2%	12·3%	927	100%
Unclassif.	43·3%	20·0%	16·9%	19·8%	1,402	100%
Whole group ..	43·4%	24·2%	17·2%	15·2%	3,717	100%
Size of group ..	1,616	896	640	565	3,717	

52·5 per cent. are diagnosed as disease of recent standing (minimal, moderate or advanced) and 47·5 per cent. as predominantly fibrotic disease. Fifty-five per cent. of adult females have recent disease.

The classification into recent and fibrotic disease was attempted despite the fact that radiological differentiation between the two can at times be difficult. The consistent variation in radiological response to treatment (Tables 8 and 10), however, suggests that such differentiation becomes a useful prognostic aid.

As will become evident, this high incidence of fibrotic disease constitutes a great obstacle to the effective treatment of pulmonary tuberculosis in the Transkeian native population.

Of 3,991 patients commencing domiciliary treatment, 1,636 had resided in urban areas for periods exceeding two months. Of these urban dwellers, 1,105 had worked underground in gold mines.

TABLE 3B.—PERCENTAGE NOT COMPLETING THIRD AND FOURTH SIX MONTHS OF TREATMENT

	Third six months' treatment		*Fourth six months' treatment*	
	No. cases treated	%	*No. cases treated*	%
Minimal	94	11·7	40	5·0
Moderate	295	11·2	97	15·5
Advanced	417	16·8	119	14·3
Gross destruction	88	14·8	31	9·7
Primary	113	15·9	36	19·5
Pleural effusion	43	23·2	15	20·0
Recent disease	477	17·8	122	15·6
Fibrous disease	425	9·8	171	12·3
Unclassified	541	17·6	116	13·0
	1,598	15·8	454	13·6

(*b*) *Disease Classification in a Few Sub-groups* (*Table* 2)

Table 2 indicates that cases are now being diagnosed earlier in the course of the disease: more now classify as having moderately advanced lesions and less as grossly destructive lesions than applied two years ago. The percentage of patients with recent disease (as contrasted with those having fibrotic lesions) is also greater now than two years ago.

This tendency towards earlier diagnosis can only be considered a favourable trend if the total number diagnosed during successive periods diminishes.

It is of interest that the ratio of cases commencing treatment to diagnosed cases who never present for treatment is relatively constant and unaffected by the disease classification. The probable explanation is that the decision to undergo treatment or not is a question, generally, of Bantu temperament rather than of any appreciation of the severity of the disease.

The small percentage with primary tuberculosis of those diagnosed by the mobile unit (as contrasted with the main group) is due to the fact that children under 10 years of age are not being X-rayed by these units.

TABLE 4.—COMPARISON OF ATTENDANCE OF THE "EX T.B. HOSPITAL" GROUP OF OUT-PATIENTS WITH THOSE WHO STARTED TREATMENT AS OUT-PATIENTS FROM THE TIME OF DIAGNOSIS

	ATTENDANCE							
	First term				*Second term*			
	No. of cases	*Class I*	*Class II*	*Class III*	*No. of cases*	*Class I*	*Class II*	*Class III*
Ex Hosp. Group	745	64·0%	23·8%	12·2%	423	57·0%	24·0%	18·3%
Non Hosp. Group	2,515	67·3%	23·6%	9·0%	1,558	56·0%	28·2%	15·2%

Attendance and Continuation of Treatment

Class I attenders—those who attend on 75 per cent. or more of all possible occasions.
Class II attenders—as above, 50 to 75 per cent.
Class III attenders—as above, less than 50 per cent.

(*a*) *Attendance during Four Successive* 6-*month Periods* (*Tables* 3*a and* 3*b*)

The overall attendance for treatment is disappointing; it is slightly better during the first six months than during the second.

As with patients failing to commence treatment, it is noted that the ratio of good to bad attenders is relatively constant and unaffected by the disease classification. The proportion who fail to complete treatment is similarly constant.

The worst offenders are the mothers responsible for the attendance of those cases with primary tuberculosis—in this group the percentage who fail to complete treatment is also the highest.

Of patients who commence treatment, 20 per cent. fail to complete the first six-month term. This figure drops to about 14 per cent. per term for the second, third and fourth six-month terms.

Table 5.—The Disease Distribution among the Absconders at the End of Four Successive Six-month Periods

	1st term	*2nd term*	*3rd term*	*4th term*
Min. T.B.	5·3%	6·5%	7·2%	4·4%
Mod. T.B. ..	26·8%	24·1%	21·3%	33·3%
Adv. T.B.	33·0%	32·1%	45·1%	37·8%
Gross destr. ..	12·3%	18·3%	8·4%	6·7%
Pleural eff. ..	3·5%	1·7%	6·4%	2·2%
Prim. P.T.B. ..	20·1%	17·3%	11·6%	15·6%
No. of absconders..	739 100%	289 100%	155 100%	45 100%

Of patients who commence treatment, 50 per cent. fail to complete the two-year period.

It has not been possible to determine the fate of these patients—the magnitude of such a task can only be appreciated if the terrain and the nature of the people is known. An attempt to achieve this will, however, be made in the near future.

(*b*) *Attendance of* "*ex-tuberculosis hospital*" *group* (*Table* 4)

These cases all belong to a group who were X-rayed at the time of the visit of the mobile unit, *i.e.* they all attended on a particular day specified two to three weeks previously. The chances were, therefore, that they would be better attenders generally—confirmed by the fact that the Class 1 attenders are higher (66·5 per cent.) than in the overall group.

The figures indicate that the ex-hospital group attends no differently from those whose treatment was instituted without prior hospitalisation.

TABLE 6.—RELATION BETWEEN RADIOLOGICAL EVIDENCE OF IMPROVEMENT AND SUBSEQUENT ATTENDANCE

Radiological changes during the 1st term treatment	*Second term attendance of first term Class I attenders*				
	No. cases	*Class I*	*Class II*	*Class III*	*Not completing*
Improved ..	304				
	100%	72·0	18·1	4·8	5·1
i.s.q.	217				
	100%	60·0	10·1	5·3	4·4
Deter. ..	25				
	100%	80·2	28·0	8·0	4·0
	Second term attendance of first term Class II attenders				
	No. cases	*Class I*	*Class II*	*Class III*	*Not completing*
Improved ..	103				
	100%	9·7	54·4	23·3	12·6
i.s.q.	77				
	100%	13·0	63·7	14·2	9·1
Deter. ..	18				
	100%	22·8	22·8	22·2	22·2
	Second term attendance of first term Class III attenders				
	No. cases	*Class I*	*Class II*	*Class III*	*Not completing*
Improved ..	31				
	100%	3·2	22·5	64·7	9·6
i.s.q.	17				
	100%	0	23·5	59·0	17·6
Deter. ..	6				
	100%	0	16·6	33·4	50·0

(*c*) *Disease Distribution among those who failed to complete the Four Successive Six-month Terms* (*Table* 5)

Table 3 indicates that the proportions of those failing to complete the various terms are very similar; Table 5, however, indicates that, of all who fail to complete their treatment, almost half classify as having advanced or grossly destructive lesions.

The difference in the percentages in Tables 3 and 5 are accepted as being due to the difference in size of the disease groups.

(*d*) *The Relationship between Radiological Improvement and Subsequent Attendance* (*Tables* 6 *and* 7)

Generally, the best attenders during the second term are those whose X-rays remained unchanged during the first term.

The worst attenders during the second term (and also the greatest percentage failing to complete the second term) are those who deteriorated during the first term.

The cases who show radiological improvement fall between the above two groups as regards their subsequent attendance.

It is suggested that those who improve feel well enough to become irregular and to discontinue their treatment, while those who deteriorate become discouraged or too ill to persevere with their treatment.

It must be noted, however, that the vast majority of patients remain in the same attendance class during the first and second terms: again a pointer that the attendance is related to temperament rather than radiological change.

TABLE 7.—SECOND, THIRD AND FOURTH TERM ATTENDANCE AND PERCENTAGE NOT COMPLETING

(Not taking first term attendance into account)

Radiological improvement during prec. term	*Second term attendance*					*Third term not completing*		*Fourth term not completing*	
	No. cases	*Class I att.*	*Class II att.*	*Class III att.*	*% not comptg.*	*No. cases*	*% not cmptg.*	*No. cases*	*% not cmptg.*
+ + +	116	53·1	17·8	21·1	8·0	123	13·5	60	11·6
+ + ..	163	45·0	33·4	11·8	9·8	105	15·2	39	5·0
+ ..	158	52·0	22·3	13·9	11·8	86	14·0	36	0
i.s.q. ..	292	59·7	23·4	9·8	7·1	182	9·9	71	14·1
Deter. ..	49	39·1	26·1	15·2	19·6	60	28·4	26	69·0

RADIOLOGICAL EVIDENCE OF IMPROVEMENT

(*a*) *The Whole Group* (*Table* 8)

It must be borne in mind that almost half of the patients in this large group had predominantly fibrotic lesions and therefore no dramatic radiological improvement could be expected. Furthermore, of the remainder with recent disease, more than half had advanced lesions.

After six months' treatment, 15·8 per cent. showed excellent (3-plus) improvement; after 12 and 18 months, 23·5 per cent. and 27·0 per cent. respectively showed excellent improvement.

If those who showed a moderate (2-plus) improvement be combined with the 3-plus group, a satisfactory improvement is found in 38·7, 43·5 and 43·6 per cent. after 6, 12 and 18 months of treatment respectively.

Considering the sub-group recent disease, 30 per cent. showed an excellent (3-plus) improvement after six months' treatment, while another 30 per cent. showed a moderate (2-plus) improvement during the same period. After a year's treatment 42·4 per cent. showed excellent clearing while 27·5 per cent. showed moderate improvement—implying a satisfactory response after a year's treatment in almost 70 per cent. of cases.

In the sub-group predominantly fibrotic disease, however, the response to treatment is entirely different: after six months' treatment only 1·8 per cent. showed an excellent response, while 60·3 per cent. remained unchanged. After 12 and 18 months the respective figures are 2·2 and 6·4 per cent. showing an excellent improvement and 53·0 and 44·0 per cent. remaining unchanged.

TABLE 8.—RADIOLOGICAL EVIDENCE OF IMPROVEMENT OF VARIOUS DISEASE GROUPS

After six months' treatment

Radiological improvement	*Min. T.B.*	*Mod. T.B.*	*Adv. T.B.*	*Gross destr.*	*Rec. dis.*	*Fibr. dis.*	*Whole group*
+ + + ..	9·3	20·9	17·5	2·0	30·0	1·8	15·8
+ + ..	14·9	21·7	29·1	12·9	30·4	9·4	22·9
+	16·8	21·5	22·2	20·7	21·9	22·3	21·3
i.s.q.	56·8	29·6	24·0	54·5	10·1	60·3	33·2
Deter. ..	2·2	6·3	7·2	9·9	7·6	6·2	6·8
Number examined	148 100%	520 100%	631 100%	203 100%	748 100%	718 100%	1,502 100%
Not examined	131	666	799	269	1,056	823	1,865

After one year's treatment

Radiological improvement	*Min. T.B.*	*Mod. T.B.*	*Adv. T.B.*	*Gross destr.*	*Rec. dis.*	*Fibr. dis.*	*Whole group*
+ + + ..	19·7	30·0	26·8	2·2	42·4	2·2	23·5
+ + ..	13·1	18·4	24·1	15·6	27·5	11·1	20·0
+	12·2	17·2	16·2	16·2	13·0	20·0	16·2
i.s.q.	55·0	25·4	20·4	44·2	7·0	53·4	28·7
Deter. ..	0	9·0	12·5	21·8	10·1	13·3	11·6
Number examined ..	106 100%	379 100%	511 100%	179 100%	621 100%	557 100%	1,175 100%
Not examined	62	239	312	121	388	352	734

After eighteen months' treatment

Radiological improvement	*Min. T.B.*	*Mod. T.B.*	*Adv. T.B.*	*Gross destr.*	*Rec. dis.*	*Fibr. dis.*	*Whole group*
+ + + ..	21·7	34·0	29·5	8·6	49·3	6·4	27·0
+ + ..	13·2	17·5	17·7	14·6	18·0	15·2	16·6
+	15·1	15·8	18·9	11·0	13·7	18·3	16·3
i.s.q.	46·7	23·2	17·7	38·5	6·3	44·0	25·5
Deter. ..	3·3	9·4	16·2	27·5	12·7	16·1	14·6
Number examined ..	60 100%	189 100%	265 100%	91 100%	290 100%	322 100%	605 100%
Not examined	24	70	98	45	119	121	237

(*b*) *The Radiological Improvement in the Three Attendance Classes* (*Table* 9)

The radiological improvement in the Class I attender is only slightly better than that in the Class III attender—the latter attends once or twice per month for streptomycin and INAH.

The percentage of Class III attenders who deteriorate, however, is more than twice the percentage of Class I attenders who deteriorate.

Whether a patient receives one, two or five injections of streptomycin per month appears to be of no consequence; the patient who takes his INAH regularly, however, is expected to do far better than the one who takes INAH for, say, one or two weeks out of every four. In an attempt to show whether

TABLE 9.—RADIOLOGICAL CLEARING OF THE THREE ATTENDANCE GROUPS AFTER SIX MONTHS AND ONE YEAR'S TREATMENT

Radiological response	*First six months' treatment*			*Second six months' treatment*		
	Class I att.	*Class II att.*	*Class III att.*	*Class I/I*	*Class II/II*	*Class III/III*
+ + + ...	16·9	14·2	15·8	25·0	24·7	21·0
+ + ...	22·8	24·0	20·2	18·2	22·2	21·0
+	20·2	22·8	23·7	16·8	18·8	19·4
i.s.q.	34·8	30·4	28·0	32·3	25·5	19·3
Deter.	5·3	8·6	12·3	7·7	8·6	19·4
Number examined ..	870 100%	382 100%	114 100%	535 100%	149 100%	62 100%
Not examined	1,057	450	243	294	75	52

TABLE 10.—COMPARISON OF RADIOLOGICAL RESPONSE BETWEEN GROUP I AND GROUP III ATTENDERS, TAKING INTO ACCOUNT THE CHARACTER OF THE DISEASE: RECENT OR FIBROUS

Radiological response	*First six months*				*Second six months*			
	Recent disease		*Fibrous disease*		*Recent disease*		*Fibrous disease*	
	Class I att.	*Class III att.*	*Class I att.*	*Class III att.*	*Class I att.*	*Class III att.*	*Class I att.*	*Class III att.*
+ + + ...	29·8	29·0	2·4	0	45·9	34·0	2·4	1·4
+ + ...	34·7	27·0	9·3	11·3	23·8	32·0	13·4	3·9
+	19·4	24·0	21·2	22·7	15·6	10·6	18·1	23·5
i.s.q.	10·7	6·4	62·0	54·7	8·1	4·2	58·0	43·5
Deter.	5·4	12·9	5·1	11·3	7·1	19·2	8·1	27·7
Number examined ..	458 100%	62 100%	420 100%	53 100%	295 100%	94 100%	281 100%	76 100%
Not examined	581	149	483	95	158	93	161	65

Class III attenders take their INAH regularly some district surgeons have kept records of INAH issues to individual patients, and the information gained is that only a small number do not require INAH as frequently as anticipated.

On the basis of attendance it was calculated that 100 patients would require only 70 patient-units of streptomycin over a given period; *i.e.* for every 100 patient-units of streptomycin approximately 140 patient-units of INAH would be required if patients were taking their INAH regularly.

(This excludes babies and young children: if these were included in the calculation the requirements would become 130 patient-units of INAH for every 100 patient-units of streptomycin.)

Drug issues in the Transkei during the past two years have been 114 patient-units of INAH for every 100 patient-units of streptomycin—this implies that patients have been using slightly more than 80 per cent. of the quantity of INAH prescribed for them. As four of every five district surgeons issue a two-to-four-week supply of INAH, it would seem that patients are, in fact, taking their INAH fairly regularly, notwithstandng any irregular attendance for weekly injections of streptomycin.

TABLE 11.—RADIOLOGICAL RESPONSE OF THE MODERATELY ADVANCED MAINLY EXUDATIVE OR RECENT CASEOUS GROUP, WHO ATTENDED 75 PER CENT. OR MORE DURING FIRST AND SECOND SIX MONTHS PERIOD

Radiological response	*First six months' treatment*	*Second six months' treatment*
+ + + ...	35·4	52·2
+ + ...	30·9	16·8
+	19·7	16·8
i.s.q.	10·3	8·0
Deter.	3·7	6·2
Number examined	188 100%	113 100%
Not examined	245	63

(*c*) *Radiological Response of Class I and Class III Attenders in two Disease Sub-groups* (*Table* 10)

The figures again indicate the similarity of response in Class I and Class III attenders, whether they have recent or fibrotic disease.

The striking difference in the responses of those with recent disease and those with fibrotic disease is also manifest.

The higher incidence of radiological deterioration among the Class III attenders—which is cause, and which effect?

(*d*) *Radiological Response of Class* 1 *Attenders with Moderately Advanced Recent Disease* (*Table 11*)

This group clears well: 66 per cent. show satisfactory improvement during the first six months and 69 per cent. during the second.

During the first six months of treatment this group forms 8 per cent. of all cases; during the second six months, only 6 per cent.

If it is accepted that the good and bad attenders do about equally well, then approximately 12 per cent. of the total on treatment during the first six months and 10 per cent. during the second can be expected to do as well as this group.

(In this group of 188 patients, 156 received 5 to 7 mg./kilo/day of INAH, while the rest received 10 to 12 mg./kilo/day.)

TABLE 12—RADIOLOGICAL RESPONSE OF A GROUP OF CASES WITH MODERATELY ADVANCED RECENT DISEASE WHO HAD 12 mg. INAH PER KILO OF BODY WEIGHT DAILY, AND 2 G. OF STREPTOMYCIN ONCE A WEEK FOR SIX MONTHS

Radiological response	*Class I attenders*	*Class I, II and III attenders*
+ + + ...	47%	33·6%
+ + ...	25%	26·1%
+	16%	22·6%
i.s.q.	3%	5·1%
Deter.	9%	12·6%
TOTAL	32	119

TABLE 13.—SPUTUM RESULTS

Sputum results at commencement of treatment

	Min. T.B.	*Mod. T.B.*	*Adv. T.B.*	*Gross dest.*	*Rec. dis.*	*Fibr. dis.*	*Total*
Cases examined ..	67	249	316	27	419	240	659 100%
% Pos. in each group	13	21	44	67	33	34	33%

Sputum results after six months' treatment

	Min. T.B.	*Mod. T.B.*	*Adv. T.B.*	*Gross dest.*	*Rec. dis.*	*Fibr. dis.*	*Un-clasfd.*	*Total*
Cases examined	68	326	352	88	475	368	360	1,194 100%
% Pos. in each group	8·8	14·1	27·3	44·4	19·6	25·6	16·1	20·5

Sputum results after one year's treatment

	Min. T.B.	*Mod. T.B.*	*Adv. T.B.*	*Gross dest.*	*Rec. dis.*	*Fibr. dis.*	*Un-clsfd.*	*Total*
Cases examined	91	348	469	175	550	540	400	1,483 100%
% Pos. in each	4·4	14·6	39·2	62·4	26·3	37·4	17·8	28·2%

(*e*) *Radiological Response of Group with Moderately Advanced Recent Disease, Receiving* 10 *to* 12 *Mg./Kilo/Day of INAH* (*Table* 12)

The figures suggest that these patients do better than those with similar lesions receiving a smaller dose of INAH.

Seventy-two per cent. of Class I attenders and 60 per cent. of all attenders show a satisfactory response to treatment.

Sputum Results (Table 13)

One specimen only of sputum was collected from patients at the time of diagnosis and/or the follow-up X-ray. Only straight smears were examined.

The disease distribution in the total 7,858 patients, and in those whose sputa were examined at diagnosis or after six or twelve months of treatment, does not differ greatly. Of those whose sputa were examined at the time of diagnosis, only 4 per cent. had grossly destructive lesions, whereas the other groups had 10 to 16 per cent. of cases with similar lesions. Had this not been so, patients with a positive sputum would have constituted more than 33 per cent. of the group.

The figures indicate that from a third to a half of positive sputa at diagnosis become negative during the first six months of treatment, but patients with advanced disease or grossly destructive lesions tend to become positive again during the second term of treatment.

Summary and Conclusions

In the Transkei 16,000 cases of pulmonary tuberculosis were diagnosed during a two-year period.

A very high percentage have advanced lesions, nearly half being predominantly fibrotic lesions.

The attendance for treatment is rather poor and a disconcertingly large number of patients fail to complete their treatment.

Patients with recent disease do well on treatment; the fibrotic group show but little clearing.

Sputum conversion of those with advanced lesions is unsatisfactory.

On the strength of available information it is not possible to predict the effect of the present approach on the tuberculosis problem in the Transkeian Territories.

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OBSERVATIONS ON LOWER LOBE TUBERCULOSIS

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Pulmonary tuberculosis rarely originates in a lower lobe, the average incidence in several reported series being about 2·5 per cent. of all cases of Pulmonary Tuberculosis. The more usual event is for bronchogenic spread to occur into a lower lobe from cavitated disease in an upper lobe, although it is not uncommon for a patient to present with coexisting disease in an upper lobe and cavitation in the apex of the lower lobe; in these cases it is not easy to say which lobe was first affected.

The rarity and special characteristics of primary lower lobe disease suggest that it may differ in its pathogenesis from the more usual reinfection type of disease starting in an upper lobe, and in order to investigate this possibility I have reviewed the literature and all cases of primary lower lobe disease which have come under my care.

Literature

Twenty series of lower lobe disease reported in the last thirty years include more than 600 patients; in these, the clinical observations were remarkably uniform, but the theories of causation varied considerably.

Clinical Reports

Lower lobe tuberculosis was found to occur almost exclusively in young people between the ages of 15 and 30 years, in females more often than males and in the right lower lobe more often than in the left. The onset was usually rapid and often acute and broncho-pneumonic, hæmoptysis being a common presenting symptom and pleurisy a frequent accompaniment. The majority of cases had early progressive cavitation of " tension " type, and where information was available there appeared to be a high incidence of endobronchitis. Rothstein (1949) found evidence of it in 75 per cent. of his 48 cases, and in most series there was a high incidence of segmental or lobar atelectasis, sometimes following the induction of artificial pneumothorax.

Theories of Pathogenesis

The pathogenesis has largely been a matter for speculation and no detailed study has been reported; Dunham and Norton (1927) felt that racial and immunological factors were important, because of the high incidence among negroes; Busby (1939) suggested that an atypical blood-borne infection might be responsible; Reisner (1935) was inclined to the view that anatomical factors caused poor aeration of the lower lobe, especially of its apical segment, and rendered it more prone to infection. This vulnerability of the apex of the lower

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lobe had been noted earlier by Kidd (1886) and Fowler (1888). Several observers, notably Colton (1928), Tirona (1940), Ossen (1944) and Hawkins and Thomas (1946), felt that rupture of a caseous gland into the lower lobe bronchus was the most likely cause.

Material

The present series comprises 30 patients with pulmonary tuberculosis in which the disease was unquestionably confined to a lower lobe or started there; these patients have been followed up for periods of from 7 to 18 years.

Clinical Features

Twenty-two patients were female and 8 were male, a ratio of three to one; the ages at onset varied from 15 to 30 years, the average being 23 years; the right lower lobe was involved in 23 cases and the left lower lobe in 7, again a ratio of three to one. The onset was usually rapid and the history of preceding symptoms never exceeded four months; in 6 cases the onset was acute bronchopneumonic in type, and they were all admitted to general hospitals and treated for pneumonia for a few days before bacteriological examination established the true diagnosis. Tubercle bacilli were found in the sputum in all but 3 cases.

Radiological Appearances

The X-ray appearances were bronchopneumonic in 20 patients; the confluent mottled shadows involved one or more of the basal segments and only rarely the apical or sub-apical segments of the lower lobe, but these were most often cavitated. Cavitation occurred in 19 patients and in each instance it was present in the first X-ray; the cavities were all large—4 cm. or more in diameter—and all but two were of tension type. Atelectasis of one or more basal segments occurred in 18 patients, and of the whole lower lobe in 2. In many, the combination of a tension cavity in the apex or sub-apex with atelectasis of one or more basal segments suggested endobronchitis of varying degree in adjacent bronchi. In 18 patients there was radiographic evidence of hilar glandular enlargement, and in 9 instances calcification appeared subsequently at the hilum. Pleural effusions occurred spontaneously at, or shortly after, the onset in 12 patients, in 4 of which they appeared to follow intrapleural rupture of a cavity; cavity rupture was confirmed in one case which was submitted to resection. Two further patients developed effusions while undergoing treatment with artificial pneumothorax. In several instances the sequence of events was clearly demonstrated radiologically, serial X-rays showing first hilar glandular enlargement followed by bronchopneumonic spread into the basal segments and segmental lobar atelectasis, often with a tension cavity in the apical segment and sometimes accompanied by pleural effusion.

Endobronchitis

Direct evidence of endobronchial disease, provided by bronchoscopy or examination of resected specimens, was found in 5 instances, and in another

subsequent tomograms showed a narrow bronchus with surrounding calcification. As bronchoscopy was done in only 7 instances and only 2 patients had resection, it is likely that such direct evidence would have been found much more frequently if it had been specially sought. If we add cases which showed tension cavities and atelectasis, singly or in combination, altogether 27 (90%) showed evidence of endobronchitis.

Tuberculin Allergy

Mantoux tests were done in only 4 patients; in one, a girl of 19, it was negative to 1/1000 at the onset of symptoms but became positive after a few weeks; in another girl of 18 the test was positive but was known to be negative two years previously. In two others, a girl of 15 and a woman of 25, very strong reactions were obtained to dilutions of 1/10,000 and 1/100,000 respectively. These findings were all suggestive of a recent primary infection.

Discussion

The striking feature about these cases is the very high incidence of endobronchial disease (90 per cent.), which agrees with Rothstein's finding of 75 per cent.

There is strong evidence that disease in the lower lobe was associated with primary infection; the occurrence in an age group in which primary infection is not uncommon, the high incidence of hilar adenitis, late hilar calcification and pleural effusion, and the Mantoux tests, in the few cases where they were done, are very suggestive.

The association of primary infection with bronchial disease supports the thesis that lower lobe tuberculosis is caused by rupture of a caseous gland into a lower lobe bronchus. This is further supported by the acute onset of symptoms and the bronchopneumonic spread in one or more basal segments. Moreover, the higher incidence of right lower lobe disease as compared with the left agrees with the higher incidence of a primary focus in the right lower lobe, as pointed out by Pagel and others, and with the greater frequency of pleural effusions on the right, as shown by Erwin (1944) and Thompson (1946).

This likelihood is strengthened by the knowledge that caseous glands frequently perforate the bronchus or the pleura. Adler and Richards (1953) found evidence of bronchial perforation by caseous glands in 57 per cent. of their cases of primary tuberculosis with consolidation or collapse consolidation submitted to bronchoscopy. Erwin (1944) gave convincing reasons for attributing primary pleural effusion to infection of the pleura from a caseating tracheo-bronchial gland.

Helleberg *et al.* (1951), reporting a series of cases of primary pleural effusion, found two distinct types. Those which had an acute onset, were slow to absorb, had a persistently raised E.S.R. and showed residual pleural thickening—in these bronchoscopic abnormalities were found in 90 per cent. In the other group the onset was slow, absorption was rapid and complete, the E.S.R. fell rapidly and no bronchoscopic abnormality was found. This finding, if con-

firmed, is important as it would provide a ready method of recognising which patients with pleural effusion have endobronchitis and are likely to develop Pulmonary lesions, most likely in the lower lobe.

Tuberculous pericardial and pleural effusions have hitherto been attributed to a latent or manifest blood stream infection, but there is increasing evidence that more often there is simultaneous perforation of a caseous gland into a systemic or pulmonary vessel and into a serous sac, causing pleural or pericardial effusion. Rich (1944), in fact, denies that pleural effusion is caused by a blood-borne infection and is of the opinion that it is always caused by the discharge of tubercle bacilli or tuberculo-protein into the pleural space.

Thus, various combinations of lower lobe tuberculosis, miliary tuberculosis, pleural effusion and pericardial effusion can be seen following primary infection, depending on which structures are eroded by the caseous glandular component of the primary complex. It is probable that disease in other lobes sometimes arises in this way but the clinical picture is never so well defined.

A case which came to autopsy and was reported by Reeves *et al.* (1942) is of particular interest. The right lower lobe was the seat of tuberculous pneumonia and contained a primary focus, the right lower bronchus was ulcerated by caseous mediastinal glands, there were widespread miliary lesions in the lungs and to a slightly lesser extent in the spleen and liver, and there were bilateral pleural effusions.

This explanation of how lower lobe lesions arise does not account for the higher reported incidence among negroes and in females, but it is probable that some immunological and hormonal factors are involved. The same factors may also be responsible for the incidence of lower lobe lesions and pleural effusions as manifestations of primary infection in adolescents and young adults rather than in young children. In the latter, however, there is also an anatomical factor; owing to the smaller size of their bronchi, *total* obstruction and atelectasis is common, and when it occurs it dominates the picture and masks any granulocaseous pneumonia which may be present, and also modifies the further evolution of the disease.

Summary

The literature relating to lower lobe tuberculosis is reviewed and a further series of 30 patients is reported.

The evidence presented supports the theory that lower lobe tuberculosis is a manifestation of progressive primary tuberculosis in young adults and is caused by ulceration of a lower lobe bronchus by caseous mediastinal glands.

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REFERENCES

Adler, D., and Richards, W. F. (1953): *Thorax*, **8**, 223.
Andosca, J. B., and Foley, J. A. (1943): *J. thorac. Surg.*, **12**, 259.
Aycock, G. F., and Keller, P. E. (1938): *Amer. Rev. Tuberc.*, **38**, 277.

BLOCH, R. G., TUCKER, W. B., and ADAMS, W. E. (1941): *J. thorac. Surg.*, **10**, 310.
BUSBY, L. F. (1939): *Amer. Rev. Tuberc.*, **40**, 692.
CHERRY, H. H. (1948): *Amer. J. Roentgenol.*, **59**, 82.
COHEN, R. C. (1943): *Brit. med. J.*, **4401**, 662.
COLTON, W. A. (1928): *U.S. vet. Bur. med. Bull.*, **4**, 503.
CROFTON, J. (1949): *Thorax*, **4**, 96.
DOCK, W. (1946): *Amer. Rev. Tuberc.*, **53**, 297.
DUNHAM, K., and NORTON, V. V. (1927): *J. Amer. med. Ass.*, **89**, 1573.
EGLEE, E. P., and JONES, O. R. (1937): *Amer. Rev. Tuberc.*, **35**, 500.
EISENSTADT, K. (1944): *Indian med. Gaz.*, **79**, 55.
ERWIN, G. S. (1944): *Tubercle*, **25**, 35.
FISHBERG, M. (1932): "Pulmonary Tuberculosis," 4th Edition. Philadelphia: Lee and Febiger.
FOWLER, J. K. (1888): "The Localization of the Lesions of Phthisis." London: Churchill.
GORDON, B., and CHARR, R. (1933): *Med. Clin. N. Amer.*, **17**, 727.
GORDON, B., CHARR, R., and SOKOLOFF, M. (1944): *Amer. Rev. Tuberc.*, **49**, 432.
HAWKINS, F. S., and THOMAS, G. O. (1946): *Tubercle*, **27**, 82.
HELLEBERG, G., *et al.* (1951): *Acta tuber. scand.*, **25**, 305.
HIDDLESTONE, H. J. H., and TAYLOR, A. J. (1954): *Thorax*, **9**, 344.
HJALTESTED, O., and TORNING, K. (1939): *Brit. J. Tuberc.*, **33**, 4.
KAYNE, G. G., PAGEL, W., and O'SHAUGHNESSY, L. (1939): "Pulmonary Tuberculosis." London: Oxford Med. Pub.
KIDD, P. (1886): *Lancet*, **2**, 615 and 665.
OSSEN, E. Z. (1944): *New Engl. J. Med.*, **230**, 693.
PAGEL, W. (1938): *Papworth research Bull.*, **57**.
REEVES, R. J., SMITH, D. T., and BAKER, R. D. (1942): *Radiology*, **39**, 467.
REISNER, D. (1935): *Arch. intern. Med.*, **56**, 258.
RICH, A. R. (1944): "The Pathogenesis of Tuberculosis." Springfield, Illinois: Thomas.
ROMENDICK, S. S., FRIEDMAN, B., and SCHWARTZ., H. F. (1944): *Dis. Chest.*, **10**, 481.
ROTHSTEIN, E. (1949): *Amer. Rev. Tuberc.*, **59**, 39.
ROZENBLAT, B. (1949): *Brit. J. Tuberc. and Dis. Chest*, **43**, 47.
STEEN, P. (1945): *Brit. J. Tuberc. and Dis. Chest*, **39**, 3.
SWEANY, H. C., COOK, C. E., and KEGERREIS, R. (1931): *Amer. Rev. Tuberc.*, **24**, 588.
THOMPSON, B. (1946): *Amer. Rev. Tuberc.*, **46**, 349.
TIRONA, J. P. (1940): *Dis. Chest*, **6**, 172.
VISWANATHAN (1936): *Brit. med. J.*, **2**, 1300.
WEIDMAN, W. H., and CAMPBELL, H. B. (1937): *Amer. Rev. Tuberc.*, **36**, 488.

Brit. J. Dis. Chest (1959) **53**, 390.

SAFE HIGH DOSAGE ISONIAZID THERAPY

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Isoniazid is of major importance in the treatment of tuberculosis and its advantages in high dosage therapy should be more widely recognised (Mitchell and Bell, 1957; Oestreicher, 1958). Such dosage carries, however, the risk of certain important toxic effects, and this has prompted clinical investigations to determine the highest dose that can be used with safety. The present paper is concerned with this problem and also reviews the literature on isoniazid toxicity.

The main effects were listed by Robitzek and Selikoff (1952) as follows:

(1) Those referable to automatic nervous system stimulation; dryness of mouth, constipation, delayed micturition, difficulties in visual accommodation.
(2) Those referable to central nervous system stimulation: vertigo, muscle twitching, hyper-reflexia, excitement, euphoria, somnolence, convulsions and psychosis.
(3) Those due to vitamin B antagonism: peripheral neuropathy, glossitis, cheilosis, pellagra and a Korsakoff-like psychosis.

The most frequent toxic reactions are peripheral neuropathy and psychosis. Other toxic effects which have occurred and are not mentioned in the above classifications are gastric intolerance, dyspnoea, optic atrophy and blindness, toxic encephalitis, blood dyscrasias and transient impairment of liver function. Allergic reactions have also occurred, such as drug fever, dermatitis and painful joints. Very occasionally kidney involvement with albuminuria and oedema has occurred. In 1953 the Committee of Therapy of the American Trudeau Society estimated that toxic reactions to isoniazid occurred in about 5 per cent. of patients and in 1 per cent. the reaction was sufficiently serious to necessitate discontinuing treatment. It is most important that toxic effects should be recognised at an early stage, when treatment is effective and more serious complications can be prevented. This has been stressed by the World Health Organisation in a recent report (1957).

Probably the commonest type of toxic symptoms described are similar to those of peripheral neuritis, and these have been described in neurological detail by Gammon, Burge and King (1953). Table I summarises the symptoms found in 74 cases of peripheral neuropathy. Numbness, tingling and burning sensations were the commonest symptoms. Table II lists the physical signs noted in the same cases. Diminution of pain, temperature and touch were commonest. Objective evidence of neuropathy is a late finding and diagnosis should be made on the earliest symptoms. Further cases have been described by Robitzek and Selikoff (1952), Heilmeyer *et al.* (1952), Klee (1952), Oestreicher *et al.* (1954), Hughes *et al.* (1954), Biehl and Vilter (1954),

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Katz *et al.* (1954), Biehl and Nimitz (1954) and Midgley and Moore (1954). Predisposing factors were alcoholism, poor gastro-intestinal function, chronic malnutrition and long standing tuberculosis.

Pyridoxine gradually emerged as the most effective drug in the prevention and treatment of peripheral neuritis due to isoniazid. Carlson *et al.* (1956) used it prophylactically with isoniazid and concluded that 25 to 50 mg. of pyridoxine and 8 to 16 mg. per kilo body-weight per day of isoniazid could be given with safety to the majority of patients. Oestricher *et al.* (1954), Tchertkoff *et al.* (1956), and Kass *et al.* (1957) also support the view that it is advisable to give pyridoxine routinely to all patients having isoniazid in high dosage. Ungar *et al.* (1954), Grunberg and Blencowe (1955), and Wasz-Hockert *et al.* (1957) agree that pyridoxine does not diminish the chemotheurapeutic properties of isoniazid.

TABLE I.—NEUROLOGICAL SYMPTOMS OF ISONIAZID TOXICITY

Authors	*Tingling*	*Pain and aching*	*Burning sensation in skin*	*Sense of electric shock*	*Soreness of muscles*	*Loss of feeling—numbness*	*Loss of balance*	*Weakness*	*Other peripheral neuritis symptoms*
GAMMON *et al.* (14 cases examined in detail)	10	6	4	4	2	10	1	1	—
KATZ *et al.* (15 cases)	15	11	15	—	—	14	—	5	—
LUBING (6 cases)	2	4	2	—	—	2	—	1	—
OSTREICHER *et al.* (8 cases)	1	—	—	—	—	1	1	1	5
TCHERTKOFF *et. al.* (Group II-18 cases)	—	1	2	—	—	4	—	—	13
JONES, W. A., and JONES, G. P. (2 cases)	—	1	1	1	—	1	—	1	—
CARLSON *et al.* (11 cases)	4	—	1	—	—	9	—	—	—

Psychosis is another important toxic effect of isoniazid therapy. This has been well described by Wiedorn and Ervin (1954). Early symptoms were those of insomnia, restlessness, irritability and increased anxiety. An acute psychosis may follow in about one month.

The true significance of these early symptoms may be missed, and the patient regarded as difficult and unco-operative, possibly leading to premature self-discharge from hospital. The acute psychosis resembles a schizophrenic-like reaction. Such cases have been described by McConnell and Cheetham (1952), Hunter (1952), Zabad (1953), Chu (1953), Vysniauskas and Brueckner (1954), Hayes (1954), Jackson (1957) and Hare (1958).

It would appear that there is no definite relation between the onset of psychosis and the duration and total dosage of the drug. The patient's personality is very important, those with unstable personalities or a history of previous mental or nervous disorders being more liable to develop psychosis.

TABLE II.—NEUROLOGICAL SIGNS OF ISONIAZID TOXICITY

Authors	*Decreased temp. pain touch*	*Dysthesia*	*Deep muscular tenderness*	*Impaired vibratory sense*	*Decreased or lost Achilles reflex*	*Hyper-active patellar reflex*	*Decreased or lost patellar reflex*	*Weakness*	*Other signs*
GAMMON *et al.* (14 cases in detail)	9	4	1	±1	7	6	2	7	—
KATZ *et al.* (15 cases)	14	4	—	3	5	6	5	5	—
LUBING (6 cases)	3	2	—	—	3	—	3	1	1 skin rash.
OSTREICHER *et al.* (8 cases)	2	—	—	—	—	—	—	1	1 nystagmus.
TCHERTKOFF *et al.* Group II (18 cases)	—	—	—	—	2	—	2	—	1 twitching of face and upper extremities and visual hallucinations. 1 twitching of feet muscles. 1 skin rash. 1 anorexia. 1 headaches. 1 stiffness of hands.
CARLSON *et al.* (11 cases)									1 optic neuritis. 1 anxiety neurosis.
JONES, W. A., and JONES, G. P. (2 cases)	1	—	1	—	2	—	1	1 bilat. wrist drop	1 diminished joint sense in toes. 1 hyperæsthesia of hands and feet. 1 sweating of palms and soles. 1 wasting muscles of fore-arm. 1 skin rash.

The schizoid personality seems to be particularly vulnerable. On the other hand, it is interesting to recall a large-scale review by Zitrin and Thompson (1956), who compared the incidence of psychosis in 19,059 patients with pulmonary tuberculosis in the year 1950 (pre-isoniazid) with 18,261 patients treated with isoniazid in 1953. There was no significant difference in the incidence of psychosis and they concluded that isoniazid did not increase the incidence of psychosis in tuberculous patients.

As the psychosis may be prolonged or irrecoverable without treatment (Hunter, 1952) it is important to give vitamin B complex at the earliest symptoms. Barbiturates have been found useful as a prophylactic in any patient likely to develop psychosis. Phenobarbitone and other anti-epileptic drugs are useful in controlling the aggravating effect of isoniazid on the convulsive tendencies of epileptics (Pleasure, 1954; Vysniauskas and Brueckner, 1954).

A pellagra state has been described in patients having isoniazid treatment (McConnell and Cheetham, 1952; Wood, 1955). Wood (1955) suggests that the saturation of the patient with nicotinic acid would lessen the possibility of toxic effects from isoniazid.

Optic atrophy, with or without blindness, has been reported as a toxic effect of isoniazid (Sutton and Beattie, 1955; Keeping and Searle, 1955). In both instances it occurred with 200 mg. isoniazid daily and the authors concluded that it was due to an idiosyncrasy to the drug. Three other cases have been reported by Carlson *et al.* (1956) and Kass *et al.* (1957). They believe that the optic neuritis is part of the toxic neuritis associated with isoniazid.

Isoniazid is claimed to have a very occasional effect on the blood. In two instances agranulocytosis has been reported by Ferguson (1952) and by Varadi and Kelleher (1953).

Watery diarrhoea with nausea and vomiting are rare manifestations of isoniazid toxicity. Rothstein and Bruce (1954) have described two patients with these symptoms. Desensitisation was successfully accomplished.

Results

We have treated to date 90 patients in hospital with the higher dose of isoniazid (Table III). A review of the literature indicated that isoniazid when given in a dosage of above 16 mg. per kilo body-weight per day caused toxic effects with some frequency. It was therefore decided to give between 8 and 16 mg. per kilo body-weight per day as the most suitable dosage range. The majority of our patients weighed between 8 and 12 stone, and we found that 600 mg. of isoniazid per day gave this range (Table IV). A few whose weights were outside the above weight range received a correspondingly higher or lower dosage.

As it was known from the literature that vitamin B given prophylactically could prevent isoniazid toxic effects, vitamin B complex tablets,* 4 to 6 daily, were given as a safeguard. In those patients whose isoniazid dosage was above

* Tab " Becosym " (Roche)—containing Aneurine 5 mg., Riboflavine 2 mg., Nicotinamide 20 mg., Pyridoxine 2 mg.

16 mg. per kilo body weight per day, or who suffered from malnutrition, long-standing tuberculosis or diabetes, a dose of 50 to 200 mg. of pyridoxine daily was given, depending on the severity of the case.

TABLE III

Ages	*Males*	*Females*
15-20 years	3	7
20-30 „	10	6
30-50 „	29	13
50-60 „	13	4
60-70 „	3	0
70-80 „	2	0
	60	30

The age and sex of the patient are shown in Table IV. The elderly patients seemed to tolerate the higher dosage well. This is important as so many tuberculosis patients are now among the older age group. The duration of high dosage isoniazid treatment extended from 3 months to 9 months (Table V).

TABLE IV

Mg. INAH per kilo body-weight per day	*Number of patients*
4-8	17
8-12	55
12-16	17
16-20	1

The initial group of patients received high dosage treatment for 3 months, but as experience was gained this period was extended. The majority of patients received the higher isoniazid dosage of 600 mg. daily for four months and then the dosage was reduced to 300 mg. daily. Some patients were allowed to continue on the higher dosage for longer periods than four months as they had

TABLE V

Duration of treatment	*Number of patients*
3 months	18
4 „	51
5 „	7
6 „	8
7 „	1
8 „	0
9 „	2

The three patients who developed toxic effects are not included in Table V.

either extensive disease with no other treatment feasible or had made better progress than was initially expected. They completed their prolonged period of high dosage without any ill effects. One male patient aged 55 years was a diabetic requiring insulin treatment (I.Z.S. Lente 20 units daily) and received 600 mg. isoniazid daily (7·8 per kilo body weight) with tabs Becosym 6 tablets daily for four months without evidence of peripheral neuritis.

In this series 3 patients showed toxic effects from isoniazid. Their case histories are as follows:

CASE 1. V.S., female, 31 years, weight 40 kilos.

She was malnourished and underweight. Both lungs were affected by tuberculosis. Treatment consisted of streptomycin 1 G., P.A.S. 10 G. and isoniazid 600 mg. daily (15 mg. per kilo body-weight per day), also vitamin B complex 4 tablets daily. Five days after commencing treatment she complained of hesitancy of micturition followed 3 days later by dryness of the mouth, constipation and twitching of the muscles of the left thigh. On examination no neurological abnormalities could be found. Isoniazid was reduced to 300 mg. daily and pyridoxine 50 mg. daily was given. After 3 days' pyridoxine treatment the symptoms had disappeared; 43 days later isoniazid was increased again to 600 mg. daily and with pyridoxine 50 mg. daily was continued for 4 months without further complications.

CASE 2. E.E., female, 43 years, weight 39 kilos.

Her general condition was poor and she was wasted. She had had extensive bilateral chronic pulmonary tuberculosis for five years and had been previously treated with combinations of streptomycin, PAS and isoniazid for prolonged periods. The tubercle bacilli in her sputum were resistant to streptomycin. She was given 50 mg. pyridoxine daily for 3 weeks before the addition of PAS 10 G., isoniazid 600 mg. daily (15.3 mg. per kilo body-weight per day) and tab. "Becosym" 6 tablets daily. After 33 days she complained of "thickness" in the throat, dryness of the mouth and tingling in the arms and legs. Hyperæsthesia was present in the wrists and hands and also on the legs. It involved both feet and legs to a distance of 2 inches above the ankles. Pyridoxine was increased to 300 mg. daily and 2 days later the hyperæsthesia had disappeared from the wrists. Injections of "Becosym"* 2 c.c. twice daily were given for 7 days and sensation returned to normal. Isoniazid 600 mg. daily had been continued throughout this period and was now continued with pyridoxine 300 mg. daily and tab "Becosym" 6 tablets daily. Two and a half months later hyperæsthesia on the ankles and feet was again noted. Isoniazid was reduced to 300 mg. daily and 2 weeks later sensation had returned to normal.

CASE 3. B.L., female, 63 years, weight 57·2 kilos.

Her general condition was good. She gave a history of a "nervous breakdown" 10 years previously. She had been treated with streptomycin 1 G., PAS 10 G., and isoniazed 300 mg. daily for 5 months. Isoniazid was increased to 600 mg. daily (10·5 mg. per kilo body-weight per day), and 2 months later she complained of twitching of the muscles around the right ankle, weakness of the

* Injection "Becosym" consists of Aneurine 10 mg. Riboflavine 4 mg., Nicotinamide 40 mg., Pyridoxine 4 mg.

legs and lassitude. Eight days later she was found to have hyperæsthesia over the dorsum of both feet. Pyridoxine 50 mg. daily was given but, in spite of this, after 2 weeks the hyperæsthesia was found to have extended to the medial side of the left arm and hand. Isoniazid was then reduced to 300 mg. daily and 3 weeks later sensation of the hands was normal and hyperæsthesia was receding on the dorsum of the feet. After a further two weeks there were no abnormal neurological signs to be found. She refused further anti-tuberculosis treatment.

In reviewing the above three cases it would appear that the clinical syndrome of toxic effects due to isoniazid is a composite picture of symptoms and signs resulting from autonomic nervous system stimulation, central nervous system stimulation and vitamin B antagonism. In Case 1 the picture was mainly that of autonomic nervous system stimulation, whereas in Cases 2 and 3 the picture of vitamin B antagonism predominated.

In Case 2 pulmonary tuberculosis was of long standing and the patient had reached a stage of malnutrition and debility as a result of self-neglect at home and premature self-discharge from several hospitals over the years. An initial period of 3 weeks' treatment with pyridoxine 50 mg. daily was given, but proved insufficient to prevent isoniazid toxic effects occurring. Although a higher dose of pyridoxine for a longer period might have been more effective, subsequent events seemed to show that this patient was unable to tolerate the higher dosage of isoniazid even when given with large doses of pyridoxine. This experience has been previously noted in the literature (Carlson *et al.*, 1956). It may be that such a patient is a " slow inactivator " of isoniazid, allowing exceptionally high blood levels to occur with consequent increased liability to isoniazid toxic effects.

In Case 3 a background of domestic difficulty and insecurity resulted in a mild anxiety state. It is difficult in this type of patient to assess the true significance of all the symptoms and signs and separate those due to her anxiety state.

Two of the above patients were undernourished and had extensive tuberculosis. We have noted in the literature that this has been a feature of those patients who develop toxic effects.

Discussion

It is noteworthy that only the free form of isoniazid in the blood is active against the tubercle bacillus (Bernstein *et al.*, 1952) and that some 30 per cent. of patients (Kass *et al.*, 1957; Bell *et al.*, 1957; and others) metabolise isoniazid so rapidly that it is impossible to achieve an effective therapeutic blood level on the standard daily dosage. In view of this, Mitchell and Bell (1957) state that until a simple routine test, possible for the ordinary laboratory, is available to detect these " rapid inactivators " it would appear wise to advise a dose of at least 12 mg. per kilo body-weight per day to all patients. They suggested that if the clinical response is not satisfactory the dose could be increased even up to 24 mg. per kilo body-weight per day. The addition of para-amino-salicylic acid is advised as this delays the inactivation of isoniazid in the liver with

resulting higher blood levels. Oestricher (1958) also emphasises that, on the average, 30 per cent. of patients are " rapid inactivators " of isoniazid as shown by biological assay methods, which have now been in clinical use since 1955. In reviewing the results in " several hundred " of his patients he noted that only one patient had a biologically effective isoniazid serum level when given a dose of 200 mg. daily. He advises that a patient under 40 years of age should be given 8 to 16 mg. per kilo body-weight per day of isoniazid with pyridoxine hydrochloride 50 to 100 mg. daily.

It is interesting to note the view of Saliba (1958), who stresses the importance of initial high dosage of isoniazid in order to avoid " therapeutic failure," and he advises the concomitant administration of PAS to make more certain of achieving adequate blood levels.

Indications for High Dosage

There are certain types of cases in which high dosage is particularly indicated. Patients with tuberculous disease amounting to more than " two zones," and those with one or more cavities, particularly with a " diameter of more than 4 cm.," are more liable to develop drug resistant tubercle bacilli (Thomas, 1958). It is possible to visualise the difficulty of attaining an effective concentration of isoniazid in the centre of a large tuberculous lesion or at the inner wall of a chronic cavity. The tubercle bacilli in these parts are reached by such small concentrations of isoniazid as to encourage the development of resistant organisms. By giving a higher dosage of isoniazid it might be possible to increase this concentration. Another important use of high isoniazid dosage is in the patient who has sputum containing tubercle bacilli partially resistant to isoniazid. These organisms, although not responding to the lower blood concentration of isoniazid, may do so to a higher concentration. It is our impression that we have achieved success in this way, but the number of cases as yet is too small to make a definite claim.

Certain patients require special consideration. The incidence of tuberculosis in the elderly is increasing, but there does not appear to be any contra-indication to the use of the higher dose of isoniazid in these patients (Pleasure, 1954). The elderly patient is frequently deficient in vitamin B as a result of poor diet. It is therefore necessary to give vitamin B complex, particularly pyridoxine, before, during and after the period of high dosage isoniazid treatment. This also applies to the patient with extensive tuberculosis, where bowel involvement by the disease or a prolonged bowel upset by PAS therapy may be a further factor. The alcoholic patient is also particularly liable to develop peripheral neuritis owing to poor diet and low vitamin B intake.

The tuberculous diabetic patient is more liable to develop peripheral neuritis because of his diabetes, and saturation with pyridoxine is important before starting isoniazid therapy. Severe peripheral neuritis may sometimes occur in a tuberculous diabetic patient treated with isoniazid, and it may be impossible to decide whether it is due to isoniazid or is, in fact, a true diabetic neuritis. Isoniazid would certainly act as a precipitating factor in this type of case (Bickerstaff, 1958).

It has been suggested that pyridoxine interferes with the therapeutic action of isoniazid, but many workers have shown that pyridoxine does not antagonise the anti-tuberculous effect of isoniazid *in vivo* (Ungar *et al.*, 1954; Biehl and Vilter, 1954; Grunberg and Blencowe, 1955).

Although this is a small series illustrating our personal experience, it has shown that it is reasonably safe to give isoniazid in a higher dose than has been usual in this country.

Saliba (1958) has suggested that the time has now come for an adequately controlled trial of "low" versus "high" dosage isoniazid treatment. We endorse this view and suggest it should be conducted on a large scale by the Medical Research Council on the lines of its previous trials.

Summary

The literature on isoniazid toxicity is reviewed.

An investigation into the safety of high dosage isoniazid treatment has been conducted. Three out of ninety tuberculous patients developed toxic effects.

Recommendations are made concerning the safest method of administering this treatment.

It is suggested that a large-scale trial to investigate fully the value of high dosage isoniazid treatment should be instituted.

REFERENCES

American Trudeau Society (1953): *Amer. Rev. Tuberc.*, **60,** 302.
Bell, J. C., Riemensnider, D. K., and Mitchell, R. S. (1957): *Amer. Rev. Tuberc.*, **76,** 152.
Benda, R., Kaufmann, P., and Buisson, J. P., (1953): *Bull. Soc. med. Hôp. Paris*, **69,** 255.
Bernstein, J., Lott, W. A., Steinberg, B. A., and Yate, H. L. (1952): *Amer. Rev. Tuberc.*, **65,** 357.
Bickerstaff, E. R. (1958): Personal communication.
Biehl, J. P., and Nimitz, H. J. (1954): *Amer. Rev. Tuberc.*, **70,** 430.
Biehl, J. P., and Vilter, R. W. (1954): *J. Amer. med. Ass.*, **156,** 1549.
Carlson, H. B., Anthony, E. M., Russell, E. F., and Middlebrook, G. (1956): *New Engl. J. Med.*, **255,** 118.
Chu, J. (1953): *West Virginian M.J.*, **49,** 125.
Ferguson, A. (1952): *Lancet*, **2,** 1179.
Ferrara, M. A., Peterson, E. B. (1953): *New Engl. J. Med.*, **249,** 1070.
Gammon, G. D., Burge, F. W., and King, G. (1953): *Arch. Neurol. Psych.*, **70,** 64.
Grunberg, E., and Blencowe, W. (1955): *Amer. Rev. Tuberc.*, **71,** 898.
Hare, E. H. (1958): *Tubercle (Lond.)*, **39,** 90.
Hayes, J. W. (1954): *Amer. Rev. Tuberc.*, **69,** 845.
Heilmeyer, L., Schaich, W., Buchegger, G., Kilchling, H., Schmidt, F., and Walter, A. M. (1952): *Munch. med. Wschr.*, **94,** 1303.
Hughes, H. B., Biehl, J. P., Jones, A. P., and Schmidt, L. H. (1954): *Amer. Rev. Tuberc.*, **70,** 504.
Hunter, R. A. (1952): *Lancet*, **2,** 960.
Jones, W. A., and Jones, G. P. (1953): *Lancet*, **2,** 1073.
Jackson, S. O. L. (1957): *Brit. med. J.*, **2,** 743.
Kass, I., Mandel, W., Cohen, H., and Dressler, S. H. (1957): *J. Amer. med. Ass.*, **164,** 174.
Kass, I., Russell, W. F., Heaton, A., Miyamoto, T., Middlebrook, G., and Dressler, A. H. (1957): *Ann. intern. Med.*, **47,** 744.
Katz, S., Gruver, R., Smith, B., and McCormick, G. (1954): *Dis. Chest*, **26,** 264.
Keeping, J. A., and Searle, C. W. A. (1955): *Lancet*, **2,** 278.
Kierch, T. A. (1954): *U.S. Armed Forces med. J.*, **5,** 1353.
Klee, P. (1952): *Disch. med. Wschr.*, **77,** 578.

LEHMANN-GRUBE, F. (1956): *Tuberkulosearzt*, **10**, 160.
LUBING, H. N. (1953): *Amer. Rev. Tuberc.*, **68**, 458.
MCCONNELL, R. B., and CHEETHAM, H. D. (1952): *Lancet*, **2**, 959.
MIDDLEBROOK, G., and COHEN, M. L., unpublished.
MIDGLEY, R. L., and MOORE, B. (1954): *Tubercle*, **35**, 508.
MITCHELL, R. S., and BELL, J. C. (1957): *New Engl. J. Med.*, **257**, 1066.
OESTREICHER, R. (1958): *Brit. med. J.*, **2**, 754.
OESTREICHER, R., DRESSLER, S. H., and MIDDLEBROOK, G. (1954): *Amer. Rev. Tuberc.*, **70**, 504.
PLEASURE, H. (1954): *Arch. Neurol. Psychiat.*, **72**, 313.
ROBITZEK, E. H., and SELIKOFF, I. J. (1952): *Amer. Rev. Tuberc.*, **65**, 402.
ROTHSTEIN, F., and BRUCE, T. H. (1954): *J. Amer. med. Ass.*, **155**, 745.
SALIBA, A. (1958): *Lancet*, **2**, 854.
SUTTON, P. H., and BEATTIE, P. H. (1955): *Lancet*, **1**, 650.
TCHERTKOFF, T., IKARD, S., ADAMSON, C., and YILMAZ, R. (1956): *Sea View Hosp. Bull.*, **16**, 62.
THOMAS, H. E. (1958): Personal Communication.
UNGAR, J., TOMICH, E. G., PARKIN, K. R., and MUGGLETON, P. W. (1954): *Lancet*, **2**, 220.
VYSNIAUSKAS, C., AND BRUECKNER, H. H. (1954): *Amer. Rev. Tuberc.*, **69**, 759.
VARADI, S., and KELLEHER, T. D. (1953): *Lancet*, **1**, 145.
WASZ-HOCKERT, O., MCCUNE, R. M., and TOMPSETT, R. (1956): *Amer. Rev. Tuberc.*, **74**, 471.
WIEDORN, W. S., AND ERVIN, F. (1954): *Arch. Neurol. Psychiat. (Chicago)*, **72**, 321.
WOOD, M. M. (1955): *Brit. J. Tuberc.*, **49**, 20.
WLD. HLTH. ORG. (1957): *Techn. Rep. Ser. No.* 141, Geneva.
ZABAD, M. (1953): *Lancet*, **1**, 295.
ZITRIN, A., and THOMPSON, D. S. (1956): *J. Amer. Assoc.*, **161**, 204.

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SPONTANEOUS LARYNGEAL PARALYSIS IN CHRONIC PULMONARY TUBERCULOSIS

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Affection of the left recurrent laryngeal nerve due to chronic pulmonary tuberculosis is thought to be extremely infrequent (Maher-Loughnan, personal communication). There is no reference to this association in the standard text-books on pulmonary tuberculosis (Goldberg, 1947; Myers and McKinlay, 1948; Marshall and Perry, 1952; Ellman, 1952; Pagel *et al.*, 1953; Hinshaw and Garland, 1956) and little has appeared on it in the English Literature apart from a short report by Radner and Snider in the U.S.A. (1952).

It is the purpose of this paper to show that laryngeal paralysis not infrequently occurs in cases of chronic pulmonary tuberculosis. An attempt is also made to explain the possible mechanism and pathogenesis in these cases.

Case Reports

Case 1. In 1951, a man, aged 58 years, was admitted to hospital with myocardial infarction. The skiagram showed cavitation in the right upper zone and some infiltration in the left lung. His voice was noted to be husky during his initial examination, but his larynx was not examined. He was presumed to have a tuberculous laryngitis.

Subsequently he was admitted several times to hospital for his pulmonary tuberculosis. In 1956 a laryngoscopy revealed that his left vocal cord was paralysed. The chest X-ray showed a cavitated lesion at the right apex with fibrosis and infiltration in the right upper zone. He had also slight fibrotic disease in the left lung. The patient is well at present and attends the Chest Clinic regularly.

Case 2. A female, aged 38, was admitted with pulmonary tuberculosis to a hospital abroad in 1956. Her chest X-ray showed an atelectatic right upper lobe with cavitation and some infiltration in left lung. There was also the suggestion of some hilar adenopathy. The right phrenic nerve was crushed during her stay in the hospital.

Hoarseness of her voice was noticed in June 1957. The laryngoscopy report stated (July 1957): " Loss of movement in the left vocal cord but the right cord moves freely. On exploration, there is a space between the cords, which accounts for the poor voice. The probable cause is pressure (by glands ?) on the left recurrent laryngeal nerve." The laryngoscopic appearance was unchanged in November 1958. Her X-ray appearance has not significantly altered since 1957.

Case 3. A male, aged 32, was diagnosed as having pulmonary tuberculosis in 1940. He was admitted to hospital in 1957, following an attack of bronchitis. Specifically questioned, he gave a history of temporary hoarseness of voice in 1953. He ascribed this symptom to excessive smoking and his voice returned to normal in a month.

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Though he had no symptoms, a routine laryngoscopy (December 1957) showed: "the left vocal cord in a cadaveric position. The right vocal cord moves freely. There is no laryngeal disease." The laryngoscopy was repeated in July 1958 and the appearance was unchanged. Bronchoscopy has so far been negative. The X-ray of his chest showed gross disease in the left lung with some infiltration and cavitation in the right upper zone. The patient has since kept well and was recently discharged home.

Case 4. A man, aged 42, was admitted in December 1957 with right-sided spontaneous pneumothorax and simultaneous loss of voice. He had had chronic extensive bilateral pulmonary tuberculosis since 1948.

Laryngoscopy report (January 1958): "Paralysis of the left recurrent laryngeal nerve. No evidence of malignant or tuberculous involvement of the cord." Following the introduction of a self-retaining Foster-Carter needle, his condition improved. His voice also improved though the paralysis of the left nerve persisted. He has since remained well.

Case 5. A man, aged 50 years, was discovered to have chronic pulmonary tuberculosis in 1948 and was admitted to different hospitals with frequent relapses since 1950.

During one of these admissions (May 1956) he developed a whispering voice. Laryngoscopy report: "the left vocal cord is paralysed; no evidence of local disease." It was suggested that the paralysis might be related to the tuberculous condition. The chest X-ray showed bilateral fibrotic disease, involving both upper zones.

The patient has been under observation since. When last seen in January 1959 he was doing well under antituberculous chemotherapy.

In none of these 5 cases was an evident cause for the laryngeal palsy discovered. A number of laboratory investigations, including W.R. and Kahn tests were negative. Special care had been taken to exclude a malignant process.

Discussion

These cases show that laryngeal palsy is not a rarity in chronic pulmonary tuberculosis. The left nerve alone was involved in all 5 cases. The laryngologists believe that thickening of the apical pleura might damage the right recurrent nerve (Scott-Brown, 1952; Thompson and Negus, 1955). The possible mechanisms of involvement of the left nerve, however, have neither been stressed nor mentioned. Before going into the details of pathogenesis it is essential to consider the anatomy of the recurrent laryngeal nerves.

Anatomy

The left recurrent laryngeal nerve arises from the vagus nerve as it crosses the arch of the aorta. It winds immediately below the arch, behind the attachment of the ligamentum arteriosum to the concavity of the arch and is related below to the pulmonary artery. The left bronchus is situated below and in front of the nerve as the latter passes in the groove between the trachea and

oesophagus and ascends out of the thorax (Gray's Anatomy, 1956). During its intrathoracic course, the nerve is intimately related to the mediastinal surface of the left lung. The right nerve, however, arises in the neck in front of the first part of the subclavian artery. As it hooks round the artery, it comes into relation with the cervical pleura.

The left nerve is related specially to two groups of lymph nodes during its course—the paratracheal and the superior tracheo-bronchial nodes. Rouviere (1938) has drawn attention to two important nodes in this situation—first, the node of the obliterated ductus, situated near the ligamentum arteriosum and secondly, the node of the loop of the recurrent laryngeal nerve.

The nerve supplies all the ipsilateral muscles of the larynx except the cricothyroid. In diseased conditions the abductor (supplied by the recurrent nerve) is the first to be paralysed and recovers last (Simon's law). Immediately following paralysis, the affected cord is median—later it slowly takes up the paramedian (cadaveric) position.

Pressure of Enlarged Lymph Nodes

The importance of this factor is difficult to assess as there is only one reported case of left nerve palsy in primary tuberculosis of children (Castells, 1948). It may be possible that the condition is not often recognised. Tuberculous abscess of lymph nodes may exceptionally involve the left nerve as was seen in an autopsy (Moore, 1918). Radner and Snider (1952) also believe that paralysis does not occur without abscess formation.

Possibly the degree of periadenitis is more important than the enlargement of the nodes themselves. The nerve and the vagus trunk survive indefinitely the pressure of massive nodes, viz. in reticulosis (Blankenhorn, 1946). However, if they are simultaneously involved in an inflammatory fibrosis, paralysis may follow (Blankenhorn, 1946). This theory partly explains the rarity of laryngeal palsy in the primary tuberculosis of children.

Chronic Mediastinitis

All five cases were suffering from long-standing, chronic pulmonary tuberculosis. All had evidence of chronic fibrosis in the lungs and in the mediastinum (as shown by the distortion of the trachea, aortic knuckle and heart shadow). The two cases of Radner and Snider (1952) also had chronic disease. It seems logical to conclude that the chronic tuberculous process might play a vital role in causing the paralysis. The intimate relationship of the left nerve to the ipsilateral lung is also to be remembered.

Chronic pulmonary tuberculosis is a well known cause of chronic mediastinitis (Marshall and Perry, 1952) and the left nerve is not infrequently paralysed in the latter condition (Myers and McKinlay, 1948). Perineural fibrosis (causing left nerve palsy) had also been observed at autopsy in tuberculous patients with pneumoconiosis (Arnstein, 1941).

This theory certainly explains the apparent rarity of this syndrome in children, who rarely develop a chronic disease like adults and it may also account for the absence of the syndrome in acute pulmonary tuberculosis.

Association with Pneumothorax

Surprisingly many cases of left-sided laryngeal palsy in association with artificial pneumothorax have been described in foreign literature (Leitner, 1938; Gualdi and Lanza, 1939; Angirany and Mouhnier-Kuhn, 1939; Champeux and Adrian, 1947; Piaget.and Seguin, 1948; di Benedetto, 1953; Ekroth, 1956; Caliceti *et al.*, 1956) against one published case-report of the same phenomenon occurring with spontaneous pneumothorax in the English literature (Palmer and Gupta, 1958).

Since the paralysis is never seen in cases of spontaneous pneumothorax in apparently healthy lungs, a basic factor should be sought. It is true that compression, displacement and overstretching of mediastinum do occur (Gualdi and Lanza, 1939), but " mediastinal cellulitis " (Caliceti *et al.*, 1956) might have been a more important factor. Thus many of the recorded cases showed fluid in the pleural space and other evidence of infection (Leitner, 1938). A mechanical injury, caused by the sudden, subclinical mediastinal shift and ischaemic damage, must have been a decisive factor in Case 4 of this series.

Other Possible Mechanisms

Unlike mitral stenosis, pulmonary tuberculosis rarely causes marked dilatation of the pulmonary artery (Fetterolf and Norris, 1911; Wood, 1956) to involve the nerve. Even in cases of mitral stenosis, Dolowitz and Lewis (1948) believe enlargement of lymph nodes to be of more importance than the dilatation of left atrium itself (Ortner, 1897).

A hypothetical toxic factor has been suggested by Castells (1948) and Portmann and Retrouvey (1935), but there is no proof of its existence.

Marked thickening of the apical pleura, associated with chronic fibrotic pulmonary tuberculosis, may affect the right recurrent nerve (Scott-Brown, 1952; Heatley, 1955; Thompson and Negus, 1955). Symptoms may then closely simulate the so-called Pancoast's syndrome (Morris and Harken, 1940).

Radner and Snider (1952) suggested that pressure of the retracted left upper lobe bronchus might damage the left nerve. Since the relation of these two is not very intimate, the mechanism is difficult to understand. Coexistent malignant disease is one of the commonest causes of the laryngeal palsy and this must be excluded.

Conclusion

In the chronic, unilateral paralysis of the recurrent laryngeal nerves, the voice may appear entirely normal (Grant, 1956). Since temporary hoarseness of voice is a very common condition (as in acute or chronic laryngitis), the acute stage may often pass completely unnoticed. The condition may be missed during a routine bronchoscopy (the operator being unaware of the condition and the cord having moved to the paramedian position). Unless chronic pulmonary tuberculosis patients are routinely laryngoscoped, the true incidence of the syndrome will remain unknown.

Because of the absence of fibrosing mediastinitis, laryngeal palsy in acute pulmonary tuberculosis should be regarded with suspicion and every care

should be taken to exclude malignancy, local pathology and other possible causes.

Summary

Five cases of paralysis of the left recurrent laryngeal nerve are described. All these patients had chronic pulmonary tuberculosis. The possible mechanisms of this association are discussed and special stress is laid on chronic mediastinitis. The literature is reviewed and it is suggested that this syndrome may be much commoner than hitherto believed.

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REFERENCES

ANGIRANY, J., and MOUHNIER-KUHN, P. (1939): *Rev. Tuberc. (Paris)*, **5**, 51.
ARNSTEIN, A. (1941): *Tubercle (Lond.)*, **22**, 281.
BLANKENHORN, M. A. (1946): "Nelson Loose-leaf Medicine," Vol. 3, p. 573. New York: Thomas Nelson.
CALICETI, G., TERGOLINA, A., and MUGGIA, G. (1956): *Minerva med. (Torino)*, **47**, 1758.
CASTELLS, R. H. (1948): *Rev. Asoc. med. argent.*, **62**, 470.
CHAMPEUX, D., and ADRIAN, E. (1947): *Ann. Otol. (St. Louis)*, **64**, 196.
DI BENEDETTO, V. (1953): *Chir. torac.*, **6**, 486.
DOLOWITZ, D. A., and LEWIS, C. S. (1948): *Amer. J. Med.*, **4**, 856.
EKROTH, L. (1956): *Nord. Méd.*, **56**, 1524.
ELLMAN, P. (1952): "Essentials in Diseases of the Chest." London: Oxford University Press.
FETTEROLF, G., and NORRIS, G. W. (1911): *Amer. J. med. Sci.*, **141**, 625.
GOLDBERG, B. (1947): "Clinical Tuberculosis," 5th ed. Philadelphia: F. A. Davies Co.
GRANT, I. W. B. (1956): "The Principles and Practice of Medicine," 3rd ed., p. 269. Edinburgh: Livingstone.
GRAY'S Anatomy (1956): 31st ed., p. 1123. London: Longmans.
GUALDI, A., and LANZA, M. (1939): *Lotta C. Tuberc.*, **10**, 314.
HEATLEY, C. A. (1955): "Textbook of Medicine," 9th ed., p. 987. Philadelphia and London: Saunders.
HINSHAW, H. C., and GARLAND, L. H. (1956): "Diseases of the Chest," 1st ed. Philadelphia and London: Saunders.
LEITNER, S. J. (1938): *Schweiz. med. Wschr.*, **68**, 747.
MARSHALL, G., and PERRY, K. M. A. (1952): "Diseases of the Chest," 1st ed. London: Butterworth.
MOORE, I. (1918): *Proc. roy. Soc. Med.*, Sec. XI, Laryngology, 167.
MORRIS, J. H., and HARKEN, D. E. (1940): *Ann. Surg.*, **112**, 1.
MYERS, J. A., and MCKINLAY, C. A. (1948): "The Chest and the Heart," Vol. I, 1st ed. Springfield: Charles Thomas.
ORTNER, N. (1897): *Wien. Klin. Wschr.*, **10**, 753.
PAGEL, W., SIMMONDS, F. A. H., and MACDONALD, N. (1953): "Pulmonary Tuberculosis," 3rd ed. London: Oxford University Press.
PALMER, H. D. and GUPTA, S. K. (1958): *Brit. J. Tuberc.*, **52**, 328.
PIAGET, A., and SEGUIN, P. (1948): *J. Med. Lyon*, **29**, 657.
PORTMANN, G., and RETROUVEY, H. (1935): *Paris méd.*, **2**, 37.
RADNER, D. B., and SNIDER, G. L. (1952): *Amer. Rev. Tuberc.*, **65**, 93.
ROUVIERE, H. (1938): "Anatomy of the Human Lymphatic System," 1st ed., pp. 91 and 99. Michigan: Edwards Bros.
SCOTT-BROWN, W. G. (1952): "Diseases of the Ear, Nose and Throat," Vol. 1, 1st ed. London: Butterworth.
THOMPSON, St. C., and NEGUS, V. (1955): "Diseases of the Nose and Throat," 6th ed. London: Cassell.
WOOD, P. (1956): "Diseases of the Heart and Circulation," 2nd ed., p. 526. London: Eyre and Spottiswoode.

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BRONCHOLITHIASIS IN A CASE OF ACTIVE PULMONARY TUBERCULOSIS

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Introduction

Although the expectoration of calcified particles is rarely encountered in clinical practice the condition has been recognised for many years. Standard medical textbooks omit the subject of broncholithiasis completely and only scattered references are found in current literature. The purpose of this paper is to demonstrate the possible clinical significance of such a condition occurring in the course of pulmonary tuberculosis.

Review of Literature

Boerhave (1744) described the case of a botanist who over many years coughed up as many as 400 broncholiths and died at the age of 54 years of "phthisis calculæ." Lloyd (1930) was able to find reports of only 18 cases of broncholithiasis in English medical literature from 1900 to 1930. He reported 4 cases of his own. Van Ordstrand *et al.* (1942) found 26 cases reported and added 2 new cases. Zahn (1946) found reports of 71 cases in the literature. He added another case. His was the first case of broncholithiasis encountered in 4,000 cases of tuberculosis at Fitzsimons General Hospital. Schmidt *et al.* (1950) presented their masterly treatise on broncholithiasis to the American Association of Thoracic Surgery, dealing with 41 cases recorded at the Mayo Clinic. Baum (1958) and others presented 2 cases of expectorated broncholiths which were proved to be caused by infection with *Histoplasma capsulatum*. The incidence of broncholithiasis among cases of active tuberculosis is extremely low. Stivelman (1928) recorded only one in 5,000 cases. Pritchard (1923) recorded two examples in 7,000 cases. The present case is the first we have encountered.

In most of the recorded cases the diagnosis was made by finding a broncholith at the time of bronchoscopy, or by surgical exploration, or by post-mortem examination. In very few cases was the coughed out stone presented for examination.

Pathogenesis

Poulalion (1891) was one of the first to describe the pathological features of broncholithiasis. He stated that broncholiths may be cartilaginous, calcareous or osseous, and they may arise anywhere in the pleuro-pulmonary tissue. They may originate (1) in the lumen of the bronchus, (2) in the bronchial wall, or (3) around the bronchus subsequently eroding the wall of the bronchus. Auerbach (1944) suggested as the cause of migration the erosion of the bronchial wall following continuous respiratory movements.

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The exact mechanism underlying the pathogenesis has never been definitely understood; it is, however, generally accepted that deposition of calcium in necrotic, inflamed or degenerated tissue is likely to cause a broncholith. The main constituents of broncholiths are calcium carbonate and calcium phosphate in the ratio found in normal bone.

Case History

K.J., 22 years, male, petty shopkeeper, was admitted in July 1958. His chief complaints were malaise, productive cough, dyspnœa on exertion and occasional hæmoptysis with severe chest pain. Pulmonary tuberculosis was diagnosed on the basis of clinical, roentgenological and bacteriological examination. In 1955 he had been a patient in some nature cure centre where he was treated with large quantities of milk (about 20 lb. a day) for about five months. He felt better and had resumed his normal work for a period of one year. Subsequently a recurrence of his old condition brought him to our hospital.

Physical examination on admission revealed a thin subject, looking very ill. The pulse rate was 100—good in volume and tension. The blood pressure was 135/95.

Clinical findings revealed restricted movements of the right hemithorax, increased vocal fremitus and bronchial breathing over the right apical and sub-apical area.

Chest X-ray revealed an extensive exudative lesion in the right upper lobe with cavitation (5 cm. in diameter). Numerous calcified plaques were seen in the lung field and mediastinum adjoining the hilar area. On the left side there was an area of infiltration extending from the left hilum to the left upper lobe. Apart from these lesions there was extensive calcification of the tracheobronchial lymph nodes. The sputum was loaded with acid-fast bacilli on direct smear.

Examination of the blood showed the hæmoglobin to be 15 g. per 100 c.c., the leucocytes numbered 9,750 per c.mm. and the differential cell count was normal.

The patient was admitted and confined to strict bed rest. Oral para-aminosalicylic acid (10 g. a day) and intramuscular streptomycin (1 g. twice a week), together with supportive treatment, were given. A pneumoperitoneum was also instituted, 700 c.c. at weekly intervals. The patient responded well and gained weight.

One month after admission he casually mentioned expectoration of a stone which he presented to the doctor on his round. It was greyish-white in colour and about 5 mm. in diameter. Its consistency was that of bone. Questioning revealed that he had expectorated broncholiths on two occasions during the last six months. Each episode was accompanied by increased frequency of an existing cough and mild hæmoptysis.

A first stage thoracoplasty was performed on August 22 and the upper four ribs were removed. The post-operative course was by no means smooth. There were persistent cough, fever and some hæmoptysis with severe pain in the chest. On the tenth post-operative day he coughed out another stone. Postero-anterior roentgenogram of the chest revealed a marked bronchial spread to the middle and lower lobes on the right side and scattered dissemination in the left lung. The patient recovered from this setback after a prolonged course of antibiotics and underwent second stage thoracoplasty on September 17. The

fifth, sixth and seventh ribs were removed and the patient recovered uneventfully.

He remains under our care ten months after the operation. Gastric washings are positive for acid-fast bacilli. The pneumoperitoneum is still being maintained.

Discussion

A broncholith may be a " silent stone " without symptoms. The symptoms, if present, may range from mild chest pain to severe " bronchial colic " and massive hæmoptysis. In our case, collapsing the cavity by first stage thoracoplasty probably caused the broncholiths to lacerate a blood vessel, thereby producing hæmoptysis and disseminating the disease to previously uninvolved lobes.

The therapeutic management of patients with broncholiths differs from that of patients with ordinary cavitary tuberculosis. In such cases techniques of pulmonary collapse like pneumothorax, thoracoplasty, plombage, etc., are unsound, because the broncholith acts like a foreign body lying in the infected space and interferes with the natural healing process. Excision of the lobe or pneumonectomy is likely to yield better results.

Whether the massive quantities of milk the patient had previously received had something to do with the formation of broncholiths or whether it was a coincidence is hypothetical. It is, however, worth quoting Morton who, in 1689, outlining the therapy of broncholithiasis stated:

> " First in the beginning of disease lubricating medicines should be used copiously; yes, and mild emetics by which one attempts to promote the expulsion of calculus . . . only when there is urgent need should a milk diet be ordered in phthisis arising from pulmonary calculi; because such a diet tends to generate new chalky stones of this kind in the lungs, whence it happens that the cure of one phthisis is accustomed to lay the foundation for another. . . ."

Morgagne (1769) agreed with Morton (1689). In support of his view he quoted Alberts Fabries, who maintained that calcareous concretions in the lungs might be increased by the use of milk. He cited the case of a patient who craved milk to such an extent that he drank it even instead of water or beer.

Addendum

This patient coughed out another stone on June 20, 1959. It was followed by a slight degree of hæmoptysis but no pain in chest.

Summary

A case of broncholithiasis occurring in active pulmonary tuberculosis is presented with therapeutic and prognostic implications.

The literature of broncholithiasis has been briefly reviewed and some of the historical features are recorded.

When surgical intervention is indicated pulmonary resection is recommended in preference to collapse procedure.

REFERENCES

AUERBACH, O. (1944): *Arch. Otolaryng. (Chicago)*, **39**, 527.
BAUM, G. L., BERNSTEIN, I. L., and SCHWARZ, J. (1958): *Amer. Rev. Tuberc.*, **77**, 162.
BOERHAVE, quoted by LEGRY (1892): *Arch. gén. Méd.*, **169**, 337.
LLOYD, J. J. (1930): "Broncholithiasis with report of four cases," *Amer. J. med. Sci.*, **179**, 694.
MORGAGNE, J. B. (1769): "The seats and causes of disease," p. 371. London: A. Miller and T. Cadel.
MORTON, Richard (1689): "Phthisiologia, sen exercitationes de phthisis tribus libris comprehensae Totumque opus historiis." London.
POULALION, S. A. M. (1891): "Les pierres du poumon de la plavre et des bronches, et la pseudophthisis pulmonaire d'origine calculeuse." Thesis, Paris.
PRITCHARD, J. S. (1923): *Arch. intern. Med.*, **32**, 259.
SCHMIDT, H. W., CLAGGETT, O. T., and MCDONALD, J. R. (1950): "Broncholithiasis," *J. thorac. Surg.*, **19**, 226.
STIVELMAN, B. P. (1928): *Amer. Rev. Tuberc.*, **18**, 430.
VAN ORDSTRAND, H. S., MOORE, P. M., and HARRIS, H. E. (1942): *Cleveland Clin. Quart.*, **9**, 36.
ZAHN, D. W. (1946): *Amer. Rev. Tuberc.*, **54**, 418.

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THE ACCEPTABILITY OF POTASSIUM PARA-AMINOSALICYLATE

By Thomas Marmion

From Killingbeck Hospital, Leeds

Though there are many different preparations and forms of PAS, each with a varying gastric acceptability, from time to time a patient presents who cannot tolerate any of the sodium or calcium salts (or derivatives) because of gastro-intestinal upset. If the potassium salt is free from such side action (as is potassium para-aminobenzoate compared with other para-amino benzoic acid compounds), there is a place for using it in the combined chemotherapy of tuberculosis. Occasionally, also, it will be of value in the treatment of patients with a restricted sodium intake, a factor of increasing importance as corticosteroid therapy becomes more generally used, and one which will facilitate the treatment of patients with circulatory insufficiency.

This short report is concerned with the gastric tolerance of the potassium salt, and not with its antitubercular effectivity, for it is known that the clinical and bateriological effects are similar to those of sodium amino-salicylate (Martindale, 1958). It should be mentioned that potassium toxicity has not been reported (Molthan *et al.*, 1955) and it has been demonstrated that higher blood PAS concentrations are found after its ingestion than after a similar dose of sodium aminosalicylate in its various presentations (Chernish and Peck, 1955).

Method and Report

Over the last year, 30 patients were treated with KPAS, as part of their combined drug treatment for pulmonary or renal tuberculosis. Some of these patients had additional tubercular lesions or other adverse conditions.

The first few patients to receive KPAS had gradually increasing doses on account of the severe symptoms they experienced with other forms of PAS. When it was realised that the potassium salt was extremely well tolerated patients were started on full dosage regardless of previous symptom severity. This was 12 G. daily over three doses, the material being made up freshly in water. When a patient had symptoms due to other PAS salts these were allowed to settle before commencing KPAS, this period being kept to its minimum.

Twenty of the patients had an uncomplicated pulmonary or renal disease and they had all previously experienced gastro-intestinal upsets of diverse severity with other forms of PAS. No such symptoms were reported following the change to KPAS, thus enabling the salt to be given for periods of up to six months.

Of the remaining 10 patients, 3 were psychologically unfit for medication

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Case	*Previous PAS*	*Reaction PAS*	*Reactions KPAS*	*Duration KPAS in weeks*	*Comments*
1	Ca PAS	Diarrhœa	None	24	
	Na PAS	Diarrhœa			
2	Na PAS	Abdominal pain	None	16	
3	Na PAS	Vomiting	None	16	
4	Na PAS	Abdominal discomfort	None	16	
5	Na PAS	Vomiting	None	14	
	Ca BPAS	Vomiting			
6	Na PAS	Abdominal discomfort			
	Na PAS (C)	Abdominal discomfort	None	14	
	Na PAS (T)	Abdominal discomfort			
7	Na PAS	Nausea			
	Ca BPAS	Vomiting	None	14	
	Na PAS (T)	Abdominal discomfort			
	PAS (E)	Abdominal discomfort			
8	Na PAS	Nausea			
	PAS (T)	Nausea	None	12	
	Ca BPAS	Nausea			
9	B-Pasinah (P)	Gastric upset	None	12	
	B-Pasinah (C)	Indigestion			
10	Na PAS	Abdominal discomfort	None	12	
11	B-Pasinah (P)	Nausea	None	12	
12	B-Pasinah (C)	Abdominal discomfort	None	12	
13	Na PAS	Nausea	None	8	
14	Na PAS	Nausea			
	PH10	Vomiting	None	8	
15	Ca BPAS	Vomiting	None	5	
16	Ca PAS	Vomiting	None	4	
	Na PAS				
17	Na PAS	Vomiting	None	4	
18	Na PAS	Nausea	None	3	
19	Ca BPAS	Diarrhœa	None	1	Hospital transfer
20	Ca PAS	Nausea	None	1	Diagnosis reversed
21	Na PAS	Abdominal discomfort	None	3	
	Ca PAS	Abdominal discomfort			
22	Na PAS	Vomiting	Palpitations	2	Three cases taken off all treatment on psychological grounds
	Na PAS (T)	Vomiting			
23	Na PAS	Diarrhœa	Diarrhœa	1	
	Ca PAS	Diarrhœa			
	Ca BPAS	Diarrhœa			
24	None		None	12	T.B. Gut
25	Ca BPAS	Diarrhœa	Diarrhœa	2	Diarrhœa present before and after treatment
26	Na PAS	Diarrhœa	Diarrhœa	1	T.B. Gut
27	None		None	12	Active gastric ulcer
28	None		Initial Diarrhœa	12	" Dumping syndrome "
29	None		Not worsened	12	Abdominal discomfort following gastrectomy
30	B-Pasinah (c)	Abdominal pain	None	8	Active duodenal ulcer

of any kind. However, as all had a definite need for chemotherapy, it was tried and success ensued in one case. One other patient in the trial could not tolerate KPAS and he was one of the three with an associated tuberculosis of the intestine; the other two tolerated the drug, one with no great alteration of the diarrhoea which was probably not related to any form of PAS. The remaining 4 patients had symptoms relative to peptic ulceration or to post-operative gastrectomy states, and they tolerated KPAS with ease. Three of these would not have had any form of PAS had it not been for the success noted with KPAS in the other patients in this small trial.

Summary

Patients who have had gastro-intestinal symptoms due to the sodium or calcium salt (or derivatives) of para-aminosalicylic acid do not have these symptoms with the potassium salt. This is remarkably well tolerated, to the extent that it may be considered for the treatment of tubercular patients with associated, or non-tubercular, gastro-intestinal disease.

REFERENCES

CHERNISH, S. M., and PECK, F. B. (1955): *Antibiot. Med.*, **7**, 377.
MARTINDALE, W. (1958): "The Extra Pharmacopœia." London: Pharmaceutical Press.
MOLTHAN, L., COHEN, R. V., and ZARAFONETTIS, C. J. D. (1955): *Amer. Rev. Tuberc.*, **71**, 220.

The potassium salt used in this trial was kindly supplied by Messrs. A. and G. Nicholas Ltd.

ABBREVIATIONS (See Table on opposite page)

PAS (T)	= Amino salicylic acid: Tablets.
PAS (E)	= Amino salicylic acid: Enseals.
Na PAS	= Sodium amino salicylate: Liquid.
Na PAS (T)	= Sodium amino salicylate: Tablets.
Na PAS (C)	= Sodium amino salicylate: Cachets.
Ca PAS	= Calcium amino salicylate: Liquid.
Ca BPAS	= Calcium benzamido salicylate: Suspension.
B-Pasinah (P)	= as powder in milk.
B-Pasinah (C)	= as cachets.
PH10	= as cachets.

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GEORGE LISSANT COX, C.B.E.

By Frederick Heaf

On September 14, 1879, George Lissant Cox came into this world to commence a life that has contributed largely to the fight against tuberculosis and is still going strong after eighty years. There will be many throughout the Kingdom and Commonwealth who will wish to pay their tributes to Lissant Cox for his great work in tuberculosis, and to congratulate him on living a truly altruistic life so full of many interests for eighty years.

Lancashire has always had a reputation for initiative, and through Lissant Cox the County Council pioneered an efficient and effective tuberculosis scheme that became a model to be studied and copied in many parts of the world. His staff worked as a team with a loyalty that could have been established only through a pervading spirit of love and admiration for their leader. For Lissant Cox knows how to guide and counsel men, and there are many committees and councils that have benefited and some that are still benefiting by his membership and chairmanship. It can be said without any hesitation that any job Cox undertakes he leaves in a better state than when he began it. Like most great physicians, his interests and energies are not confined to medicine. Today he can still land a 10 lb. salmon with the ease and grace of an accomplished angler. His knowledge of apples and orchards is equal to and surpasses that of many professional horticulturists, so much so that he is regarded not only as a consulting physician to some sanatoria but also as their " honorary pomologist." Being a true *bon viveur* with an intimate and discreet knowledge of the wines of France—often knowing which side of the fence the grapes grew—his hospitality is liberally and carefully arranged and is a delight to all who are fortunate to experience it.

When Lissant Cox retired from his official duties in the tuberculosis field all his many friends were happy to see that his labours were recognised by the conferring on him of the order of C.B.E., an honour that his work richly deserved. Since then he has lived at the foot of Caer Caradoc in the beautiful country around Church Stretton that he appreciates and knows so well. He still pays frequent visits to London to attend committees, where with piercing insight he pleasantly unravels perplexing problems and gives sound and clear guidance to confused chairmen and bewildered members.

This lovable and vital man is now 80. We wish him and Mrs. Lissant Cox many years of continuing joy and happiness. May they still come to our meetings and conferences and enhance our social events with their gracious company.

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SIR ROBERT YOUNG, C.B.E.

By G. E. Beaumont

On Saturday, August 22, Sir Robert Young passed peacefully away in his eighty-eighth year, and all readers of our Journal, together with countless other doctors, patients and friends in various parts of the world, will mourn their loss.

Sir Robert took a great interest in our Journal and knew intimately the successive editors, Dr. T. N. Kelynack, Dr. L. S. T. Burrell, Dr. Clifford Hoyle, and our present editor Dr. Philip Ellman. Sir Robert found time to contribute several articles to the Journal. In the Golden Jubilee Number of January 1956 he gave a masterly survey of the medical problems of tuberculosis and diseases of the chest which had confronted chest physicians during the last fifty years. He concluded on an optimistic note, " In general it would appear that the outlook in diseases of the chest, including tuberculosis, is a hopeful one."

In January of this year Sir Robert published his last contribution to our journal, writing, in a series by eminent members of the profession, his congratulations on the occasion of the Journal changing its name from " The British Journal of Tuberculosis and Diseases of the Chest " to " British Journal of Diseases of the Chest." In 1943 the Journal had added " Diseases of the Chest " to its original title of " The British Journal of Tuberculosis." Sir Robert now expressed the view that " a change of name does not indicate a change of policy but an adjustment of perspective. Tuberculosis is still a national and even more an international problem." In witness to this is the influx of so many natives from the Dominions, without a medical examination.

Sir Robert, or " R.A.," as he was affectionately known to generations of Middlesex students, was one of the great clinical physicians of our time, who placed the art of medicine first and the accessory aids to diagnosis second. During his later years he was recognised as the leading chest physician in this country.

On the occasion of his eightieth birthday I wrote an appreciation of R.A. which was published in this Journal, and I endeavoured then to express the high regard in which he was held by the medical profession in general, and my personal indebtedness to him for the inspiration gained during my close associations with him, first when a student at Middlesex, and later as his house physician and assistant physician at Middlesex and Brompton.

I was first attracted to R.A. when I was a student at Middlesex on account of his powers as a teacher and diagnostician. On his ward rounds he would deal with one case thoroughly, demonstrating how much information could be obtained by taking a careful history from the patient and by a meticulous clinical examination. In those days there were not many X-ray examinations, and the application of Biochemistry to Medicine had not arrived.

As his house physician he would leave me to work out a difficult case, and on his next visit he would examine the patient himself and draw his conclusions, and then compare his findings with mine.

I owe my introduction to Brompton to R.A. Towards the end of my six months as house physician at Middlesex, he asked me at the end of a ward round on a Friday afternoon if I would like to go with him to Brompton to see a post-mortem examination on one of his patients. I was delighted at the opportunity, and, on the way in a taxi, R.A. said that the case was very interesting and that he had made the diagnosis of mediastinal tumour. We went to the post-mortem room and found the examination had been completed. The lungs revealed the presence of a tumour encroaching on the mediastinum. The growth was probably a bronchial carcinoma, but in those days a bronchial carcinoma was not a recognised condition and many cases which formerly would have been called mediastinal tumour or mediastinal cancer were shown later to be bronchial carcinoma. I was much impressed with R.A.'s diagnostic skill, and when, on the way back, he asked me if I would like to apply for his house physician's appointment at Brompton, which would be vacant in a few weeks' time, I accepted with alacrity.

Later he introduced me to medical writing by collaborating with me, shortly after my appointment to the staff of Middlesex and Brompton, in writing the section dealing with Diseases of the Lungs in *Price's Medicine*. The only time which R.A. had available for this was late at night, and I used to dine with him at Harley Street one or two evenings a week. At about 9 p.m. we would settle down in his consulting room with cigars and coffee and go over what we had written, and at about 11 p.m. his kindly and devoted wife would come in with a tray of refreshments and tell us it was time we stopped—much to my relief. R.A. was very careful in all he wrote, and we would spend much time discussing whether we should put in or leave out certain minor details of treatment. We were subsequently associated with this section in *Price's Medicine* in all its editions.

R.A. was also a first class postgraduate teacher at Brompton. In the periodical courses held there before the Second World War his demonstrations were most popular—he was not a showman, as were some of the well-known London physicians at that time, but he emphasised in his postgraduate teaching, as he did to his undergraduates, the importance of the clinical examination and the deduction of the diagnosis from the facts observed and elicited.

All his hospital patients were treated with courtesy and consideration, and he insisted that his staff should do the same. In the cold weather at Brompton—and in the wards with the windows wide open, and little or no heating, it was bitterly cold—the staff nurse used to carry round a rubber hot-water bottle wrapped up in a shawl, on which R.A. warmed his hands before applying them to the patient's chest.

R.A. was undoubtedly one of the very great physicians we have had at Middlesex and Brompton, standing in a class of his own, but despite his numerous distinctions he always remained friendly and readily accessible.

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REVIEWS OF BOOKS

The Ecology of Human Disease. By JACQUES M. MAY, M.D. New York: M.D. Publications Inc. 1958. Pp. xxiii + 323. $7.50.

This book is the first of a three-volume study in medical geography, made under the auspices of the American Geographical Society. The author makes the comment in a brief preface that the book was difficult to write because it is intended to be useful to physicians, geographers, and anthropologists.

The first seven chapters are devoted to the nature of disease with particular reference to physical, organic and cultural influences, and these are followed by a detailed study of the ecology of various diseases, including tuberculosis. The chapter on this disease begins by discussing the general pathology before turning to the geographical distribution. It is inevitable that some countries, for example the United States, should receive more detailed consideration than others, which may only occupy a line or two. The statistics given for England include the following:

"The most heavily infected areas in England are the counties of Anglesey, with 91·6 death rate per 100,000, and Merionethshire with 92·8 per 100,000. The city of London comes next, with 70·2 per 100,000. On the other hand, most of the country has a rate of 30 to 50 per 100,000; some privileged areas, such as the Isle of Ely, have a death rate between 20 and 30 per 100,000. Even inside the city of London, rates range in different boroughs between 118·1 in the city proper to 27·9 in Hampstead" (*sic*).

Scotland and Ireland are dealt with separately, but not Wales, although there is a reference, under the heading of the Belgian Congo, which begins: "A tuberculin survey has been made in the part of the Belgian Congo called the Rhondda Fach."

The latter part of the chapter is devoted to a review of the position of B.C.G. vaccination, based primarily on W.H.O. statistics up to 1956. In conclusion it is emphasised that "the only factor that is not likely to be changed in the parts of the world where tuberculosis is still an important problem is the way of life and the diet. On this score the future is dim indeed for the underdeveloped countries, but it can be hoped that before new strains develop, considerable improvement in the disease map will occur because of the progress made in prevention and treatment."

An immense amount of labour has been put into this book. Its chief value to the medical man is as a source of reference on the relative importance, in different parts of the world, of the various diseases discussed.

A. LESLIE BANKS.

The Chemistry and Chemotherapy of Tuberculosis. By ESMOND R. LONG, Henry Phipps Institute, University of Pennsylvania. 3rd edition. London: Baillière, Tindall and Cox. 1958. Pp. 450. 96s.

The chemotherapy of tuberculosis was in its infancy when the first edition of this well-known book was published in 1923. This third edition has been completely rewritten by Professor Long and appears at a time when interest in anti-tuberculous drugs is greater than at any time in the past. These substances

are described individually in the third section of the work preceded by sections dealing respectively with the chemistry of *Myco. tuberculosis* and the changes it may produce in the host. The chemical changes which occur in infected and non-infected tissues are described separately with particular attention given to hypersensitivity. The chapters describing the chemical changes in blood, effusions, sputum and urine summarise valuable data for easy reference.

The antibacterial treatment of tuberculosis is still largely empirical in spite of the accumulation of detailed knowledge about the composition and metabolic activity of the tubercle bacillus. Such ways in which the effects of applied therapy may be aligned with the physiology of the causative organism are made the more apparent by this reference work. Professor Long's vast personal experience in this field gives balance to a text which is presented in short chapters, subdivided for added clarity, and having extensive up-to-date references.

R. W. RIDDELL.

The Bacteriology of Tuberculosis. By EGONS DARZINS, M.D., Anoka State Hospital. Minneapolis: University of Minnesota Press, 1958. Pp. 488. 80s.

This publication reflects Dr. Darzins' wide experience with the bacteriological aspects of tuberculosis, gained in many parts of Europe and the United States. The work contains much variety of subject matter, each aspect being introduced by historical data. A valuable feature is the frequent comparison made between the behaviour of mycobacteria and other bacterial genera. The book is divided into five parts, of which the first two deal with the cytology and growth requirements of *Myco. tuberculosis*, the third with the isolation and identification of mycobacteria, the fourth with typing and virulence and the fifth with experimental infections. In the last, laboratory hazards and precautions are discussed and there is an unusual account of instances of premeditated self-inoculation with the tubercle bacillus. The value of the safety hood fitted with adequate exhaust ventilation is dismissed too lightly. The metabolism of *Myco. tuberculosis* is summarised so as to give a useful introduction to those interested in the mode of action of anti-tuberculosis drugs. Fluorescence and electron microscopy are described in detail. There is a bibliography of sufficient magnitude giving titles of the references.

Dr. Darzins' book is readable and informative and is presented in a way which should prove widely acceptable both to laboratory workers and clinicians in the field of tuberculosis.

R. W. RIDDELL.

Les Nouveaux Termes Anatomiques. Lexique Conforme à la Nomenclature Internationale (P.N.A.). By GEORGES OLIVIER, Professeur Agrégé à la Faculté de Médicine de Paris. Preface by Professor DELMAS. Paris: Vigot Frères. Pp. 146. Fr.800.

Anatomy has suffered for years from the lack of a common terminology. A World Commission, under the auspices of U.N.E.S.C.O., studied the subject for five years and reported to the Sixth International Congress in Paris in 1955, when an agreed nomenclature, the Parisiensa Nomina Anatomica, was put forward.

The present volume is a dictionary of anatomical terms, based on the

P.N.A. It presents the French name, the international equivalent in Latin and a "free" translation of the Latin into French. For instance, "Nœud de Keith et Flack—Nodus sinu-atrialis—Nœud sinu-atrial."

It is impossible to review a dictionary. The book will be useful to French students of anatomy for reference when they are confused by the use of unfamiliar terms.

L'Acupuncture devant Le Bon Sens et la Physiologie des Points Cutanes Sensibles Couples. By JEAN-PHILIPPE CROUZET. Paris: Vigot Frères. 1959. Pp. 134. Fr.1,300.

This is an extraordinary book. The author began to study the subject by accident and his interest was aroused to such an extent that he has taken a great deal of trouble to investigate the phenomenon which he calls "associated sensitive spots."

When he was a boy the author had noted the occurrence of sensory disturance at a distance when he happened to scratch his skin. He has now carried his observations much further, and he has listed a great number of points on the skin of all parts of the body from which, as the source of the primary stimulus, he is able to elicit subjective sensory responses at a distance.

He considers that the existence of this coupled sensitivity plays an important role, through involuntary muscle contraction, in preventing skin trauma. He goes so far as to put forward the suggestion that it is this mechanism which guarded primitive man from the fatal effects of injury and of various bacterial infections.

He correlates his work with that of the ancient Chinese, who made extensive use of acupuncture in treatment, and he concludes that the beneficial results of acupuncture are in some way connected with the existence of these coupled sensitive spots. In his view acupuncture is simply a variety of physiotherapy.

JAMES MAXWELL.

Aviation et Tuberculose Pulmonaire. By PIERRE WEILLER, Médecin Assistant à l'Hôpital Laennec. Preface by Professor ROBERT MONOD, Membre de l'Académie Nationale de Médecine et de l'Académie de Chirurgie. Paris: Vigot Frères. 1958. Pp. 232. Illus.

Air travel is now so universal that the relation of altitude to physical fitness demands increasing attention.

The author of this volume considers some of the problems of aviation with special reference to tuberculosis, although he properly includes other diseases of the lungs and refers briefly to the heart and circulation as well.

He considers his subject first from the point of view of the air-crew, and he concludes that pulmonary tuberculosis in flying personnel does not differ appreciably from the disease which is familiar to all practitioners. The usual factors are present, but they may be aggravated by the effects of repeated sudden changes in atmospheric pressure.

From the point of view of the passenger, either civil or military, the problem is slightly different. For instance, eighth nerve impairment, as a result of streptomycin treatment, might be a contra-indication to flying. On the other hand an artificial pneumothorax, properly controlled, is likely to be quite safe.

Pneumoperitoneum is also well tolerated at an altitude. Respiratory complications of tuberculosis, and other lung diseases, must be considered according to the merits of each case.

Increasing experience has shown that air travel is better tolerated by patients with most forms of respiratory and cardiac disability than was considered to be the case a few years ago. The author concludes by quoting the dictum of MacFarland, " if you can walk you may fly."

La Corticotherapie surrenale dans le Traitement de la Tuberculose. By C. GERNEZ-RIEUX, H. WAREMBOURG and M. PAUCHANT. Pp. 176. 35 illustrations.

The authors point out that there has been a change of opinion about the influence of the corticosteroids on tuberculosis of the lung. At first it was generally accepted that cortisone was contraindicated in the presence of tuberculous infection. This view was subsequently modified, and the results of the recent observations appear to suggest that there are certain circumstances in which cortisone therapy may be beneficial.

After a study of more than 500 patients it is concluded that cortisone is indicated in the treatment of sero-fibrinous pleurisy and similar conditions affecting the other serious membranes. It is also of value in miliary and other acute forms of tuberculosis. The indications in chronic tuberculosis are not so clear.

There are certain general contraindications which must always be kept in mind. In the first place there are the general diseases, hypertension, gastric ulcer, diabetes, psychotic disturbances, amyloid disease and venous thrombosis. There are also certain special contraindications to cortisone therapy in tuberculous disease. Cortisone should not be given unless it is known that the tubercle bacilli are reasonably sensitive to isoniazide. In any old-standing or incompletely treated tuberculosis sensitivity of the bacilli must always be demonstrated before corticosteroid therapy is instituted. In recent cases, however, the authors are prepared to take the slight risk which is run by commencing treatment at once, without waiting for the results of the laboratory tests.

On the whole it appears that treatment with cortisone is a useful adjuvant to chemotherapy of tuberculosis in carefully selected cases.

JAMES MAXWELL.

BOOKS RECEIVED

The following books have been received and reviews of some of them will appear in subsequent issues.

Textbook of Medicine. By R. L. Cecil and R. F. Loeb. 10th edn. London: W. B. Saunders and Co. Ltd. Pp. 1,660. £5 15s. 6d.

Brompton Hospital Reports, Vol. XXVII, 1958. Lloyd-Luke (Medical Books) Ltd. Pp. 276. 15s.

Social Work in Tuberculosis. By Margaret Coltart, Helen Raine and Elizabeth Harrison. London: Chest and Heart Association. Pp. 144. 12s. 6d.

Postural Drainage and Respiratory Control. By E. Winifred Thacker. 2nd edn. Lloyd-Luke (Medical Books) Ltd. Pp. 62. 10s. 6d.

Papers dedicated to Dr. Kjeld Torning on his 60th Birthday, June 29th, 1959. Copenhagen: Ejnar Munksgaard. Pp. 240.

A Clinical Study of the Hæmagglutination Reaction in Tuberculosis. By Jan. Spangberg. Copenhagen: Ejnar Munksgaard. Pp. 96.

Die Streifenatelektasen der Lunge. By Priv.Doz. Dr.Med. Friedrich Heuck. Stuttgart: George Thieme. Pp. 108. Illus. DM. 32.

Das Rontgenschichtbild. By Prof.Dr.Med. A. Gebauer, Doz.Dr.Med. E. Muntean, Prof.Dr.Med. E. Stutz, Prof.Dr.Med. H. Vieten. Stuttgart: George Thieme. Pp. 454. Illus. DM. 148.

Handbuch der Urologie. Bd. 9/2. *Inflammation* 11. Editors: C. E. Alken, V. W. Dix, H. M. Weyrauch, E. Wildbolz. Berlin: Springer. 90 figs. Pp. 564.

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REPORTS

RECENT TRENDS IN THE TREATMENT OF TUBERCULOSIS

By Drs. J. L. Blaisdell, H. S. Coulthard, G. L. Gale, D. R. Garrett and C. A. Wicks

The 55th report of the Toronto Hospital surveys recent trends in their treatment of pulmonary tuberculosis, and extracts of some of their observations should be of interest to British readers.

(*a*) *In Sanatorium*

Chemotherapy

Throughout 1958 the policy of using three drugs concurrently (SM, PAS, INH) unless otherwise indicated was continued. This regime has been in use since 1952 and has reduced the number of drug failures to a very small figure. Its value was indicated when a group of patients was treated on two drugs alone, Na PAS and a hydrazide of INH, between June 1957 and December 1958. The rate of recovery was delayed in this group and the need for surgery of residual lesions was much higher than in the other patients who were on triple chemotherapy.

Dosages

The usual dosage in use is INH 300 mg. daily, Na PAS 14 g. daily, and streptomycin sulphate 1 g. twice a week. A considerable number of cases of advanced tuberculosis or miliary disease are given streptomycin *daily* for three months. Many forms of PAS are in use, in order to obtain patient acceptance of this rather unpalatable substance. Despite the fact that Calcium B PAS does not give tissue levels or urinary levels of PAS comparable with those obtained from sodium PAS, it is unhesitatingly used in cases of intolerance of sodium PAS, and INH resistance has not resulted. Patients who show a low urinary excretion of free INH are given an increase of dose up to 600 or 900 mg. daily, to obtain higher levels. Patients who show signs of peripheral neuritis or mental excitation are treated by substituting Compound 377 (a hydrazide of INH) for INH itself, and are able to continue on this form of therapy without necessarily having recourse to pyridoxine.

Other drug regimens are sometimes used in treatment failures where the tubercle bacilli show resistance to one or more of the three main drugs. None of these subsidiary drugs is as effective as streptomycin or isoniazid and there have been few, if any, sputum conversions with their use. Their main value is for short-term protection during some particular crisis such as a pulmonary resection.

Pyrazinamide is undoubtedly the best from this point of view. It has been used in 71 drug resistant cases undergoing pulmonary resection. It is usually given for 3 months at a dosage of 40 mg. per kilo body weight, and has proved to be effective, and at this dosage without serious toxicity.

Viomycin was given to two patients during 1958 and intravenous PAS to one.

Oxamycin (*Cycloserine*): After three years of trial of this drug in " treatment failures," we have come to the conclusion that its usefulness is very limited. It is given in the dosage of 0·25 g. four times a day and great care must be taken to space the dosage evenly or convulsions may occur. Eight cases received this in 1958 but none showed any marked benefit.

Cortico-steroids: Fifty-seven patients received steroid therapy in 1958, concurrently with anti-tuberculosis drugs. In a majority this was given for treatment of active tuberculosis or the toxic complication associated with chemotherapy of tuberculosis. Prednisolone (or metacortone, colisone or hydrocortone) was used until the end of the year, when one of the newer steroids like Decadron came on to the market. The results of treating florid and fulminating cases of pulmonary tuberculosis with steroids were very satisfactory, and the dosage recommended by the Medical Research Council of Great Britain was followed.

(*b*) *After Discharge from Sanatorium*

Chemotherapy

In these days of shortened hospital treatment much reliance is placed on patient co-operation to continue taking chemotherapy at home in order to complete the recommended course. To make domiciliary treatment easier, streptomycin is discontinued at the time of discharge, unless the bacilli are known to be resistant to PAS or INH. As a matter of fact, a recent survey has shown that very few patients become resistant to these two drugs, although many do to streptomycin. Whether the patients actually take the drugs at home is uncertain. It is customary to provide a three month supply when the patient is discharged, with arrangements for further supplies to be picked up every three months for as long as is recommended. In January 1958 a scheme was drawn up for recording the approved length of treatment of each discharged patient, with provision for recording each time the patient returned to hospital for a new supply of drugs, on the assumption that if a new package was picked up at the end of three months the supply for the preceding three months had actually been consumed. In spite of fallacies in this reasoning, it is possible to estimate the degree of patient co-operation. If no drugs are called for it is safe to assume that the drugs are *not* being consumed, because patients do not decline to accept free drugs from the hospital and proceed to buy them at their own expense—unless they were leaving the hospital against advice. Excluding those who did actually leave against advice, or were transferred to other hospitals, or were the responsibility of the D.V.A., there were 553 patients who were discharged in 1958 on chemotherapy, and were expected to return to this hospital for new supplies of drugs. The recommendations of the medical staff for continuing chemotherapy at home covered periods of time varying from three months to " indefinitely." The percentage of patients in each three months period was as follows: 3 months 2%; 6 months 12%; 9 months 33%; one year 40%; 15 months 5%; 18 to 24 months 4%; " indefinitely " 4%. This indicates that 73% of discharged patients were expected to continue

chemotherapy at home for 9-12 months. Did they actually do this? Taking February 15, 1959, as the "cut-off" date, only 281 of the 553 had been away from sanatorium long enough to have completed the recommended course.

The total duration of chemotherapy recommended has been equal to and usually in excess of twelve months since 1952. During 1958 varying periods of chemotherapy are recommended according to individual indication and circumstances. The "average" total duration of chemotherapy (in sanatorium and post sanatorium) is approximately eighteen months to two years. As the duration of treatment in sanatorium has decreased, the duration of post-sanatorium chemotherapy has increased.

Relapse Rates

During 1958 the follow-up study on "adequately treated" patients with pulmonary tuberculosis was completed.

Six hundred and forty-eight patients with pulmonary tuberculosis who had completed one year (or more) of chemotherapy *in sanatorium* were followed for at least two years and a maximum of four and a half years.

In this time 20 cases (3·1%) had relapsed and a further 5 were readmitted with recurrence of pulmonary symptoms but without proof that these were based on reactivation of pulmonary tuberculosis.

The relapse cases were studied in detail. The age range was 22 to 67 years, and 10 of the 20 cases were aged 40 years or less at the time of relapse. Eight were female and 12 were male patients.

Of the 20 cases, 14 had cavitation and in 8 the disease was far advanced at the time of original admission. In 10 the disease was moderately advanced. Only 1 patient had a resection (lobectomy) performed at the time of original treatment. In the 20 relapse cases, sensitivity to the drugs was complete in 11 cases, unreported in 3 and in 2 tubercle bacilli were not cultured. Partial resistance only to one drug was encountered in the remaining 4 patients. In 4 of these patients resection was recommended but not performed for various reasons.

Pregnancy in Tuberculosis. Even before chemotherapy was available it was felt that if both pregnancy and tuberculosis were adequately treated, only an occasional border-line case would be benefited by therapeutic abortion. There is even less indication for this now, when the prognosis in pulmonary tuberculosis has been so greatly improved. As it is now believed that streptomycin during pregnancy has no deleterious effect on the fœtus, routine chemotherapy is used for the mother's disease. Post-partum pneumoperitoneum has not been used in Toronto for many years. Thoracoplasty, resection or nephrectomy can be carried out in the second trimester if strictly necessary. As normal cases are delivered on the ward which has been their home for some months, they are not disturbed by sudden change in their surroundings at the onset of labour such as would be encountered by transfer to a busy obstetrical service in a general hospital and this, with increased rest, may be the reason for the relaxation encountered in most of these cases, as labour is usually short and little anæsthesia required after preliminary medication with demerol and hyoscine.

Artificial Pneumothorax and Pneumoperitoneum

Because of the efficacy of long-term chemotherapy in treating reversible pulmonary tuberculosis, temporary collapse has not been used for some years. No pneumothoraces have been established in the past five years and tuberculous empyema has accordingly become a rarity. Therapeutic pneumoperitoneum has not been attempted in the past three years as it appeared to add little benefit over chemotherapy alone.

Pulmonary Resection

Excision therapy continues to be used with only slightly reduced frequency. In 1958 there were 54 resections on 53 patients (one was bilateral) and also 7 decortications. Chemotherapy alone is used for small isolated lesions, stellate scars from former cavities and areas of fibrosis with or without bullous emphysema. The main indications for resection are large areas of irreversible destroyed lung, persistent cavities, large nodules of caseation and bronchostenosis. Of the 54 resections only 10 came to operation with positive sputum. Three of these developed bronchopleural fistulæ and one developed a post-operative spread of disease, but fortunately all responded well to treatment. The majority of resections had chemotherapy for 6-9 months before operation, but it is possible to operate earlier on solid lesions which change little under chemotherapy. The minimal stay in hospital is three months after operation and all are given drug treatment at home.

Thoracoplasty

The unhealed apical lesion is usually resected, so there is now little call for thoracoplasty. In 1958 there were no standard thoracoplasties but there were 4 post-resection thoracoplasties, 3 for bronchopleural fistula and one following lobectomy with segmental resection.

Cancer of the Lung

During the past year an increasing number of cases of malignant disease have been recognized through laboratory investigation. The majority of these were, of course, primary carcinoma of the lung, but several cases of other types of malignancy have also been discovered. Exfoliative cytology has proven of great value in the examination of sputum, bronchial secretions and body fluids. The technique of fixation in Bouin's solution, paraffin sectioning and staining with hematoxylin and eosin is preferred to the Papanicolaou method. The examination of small amounts of secretion obtained through the bronchoscope has not proved as successful as the study of serial sections of relatively large amounts of sputum expectorated directly into Bouin's fixative over a period of three or more days. This procedure can be recommended also for the recognition of pathogenic yeasts and fungi and during the past year established the diagnosis in a case of unsuspected pulmonary blastomycosis when other methods had failed.

Scalene node biopsy has confirmed the diagnosis of either tuberculosis, sarcoidosis or malignancy in a number of cases and is a valuable procedure employed with increasing frequency. Needle biopsy of the lung or pleura or biopsy by open thoracotomy are occasionally but not widely employed.

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NOTES AND NOTICES

WELLCOME HISTORICAL MEDICAL MUSEUM

Collection of Pneumothorax Machines

There is being formed at the Wellcome Historical Medical Museum a collection of pneumothorax machines and needles illustrating the various models from the time of the first Forlanini instrument to those invented in the 1940s.

The nucleus of this collection is at present in Leeds and will be shown, before its transfer to the Wellcome Historical Museum, at a meeting of the British Tuberculosis Association and the Yorkshire Thoracic Society in September 1959. The present collection is nearly complete as regards English models of machines and is complete as regards English needles.

If any readers have Continental, American or English apparatus that is no longer required, Dr. Thomas Marmion would be grateful for their loan for the Leeds exhibition; or their gift for the same reason prior to their transfer to the permanent collection to be kept in London. Dr. Marmion can be contacted at Killingbeck Hospital, York Road, Leeds 14.

T.B. VACCINATION EXTENDED

For Further Education Students

Older children and students attending universities, teacher training colleges, technical colleges and other establishments of further education may now be offered vaccination against tuberculosis.

This extension of B.C.G. vaccination, at present limited to schoolchildren between 13 and 14, has been decided on by the Minister of Health, who has informed local health authorities that he is prepared to approve such arrangements. The Minister is also prepared to approve arrangements for the offer of vaccination to whole school classes where convenient, even though a few of the children are under 13 years of age.

Since 1949, when official permission for its use in this country was first given, B.C.G. vaccination has been offered to all nurses and medical staff in hospitals and (at the discretion of chest physicians) to the close home contacts of tuberculosis cases.

While drawing the attention of local health authorities to this decision the Minister of Health has also emphasised the importance of the maintenance of tuberculosis registers in controlling the disease. Such records enable the Medical Officer of Health to study the pattern of the incidence of the disease and to take appropriate action when a significant grouping by residence, occupation or family is noted.

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